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(54) **Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel.**

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I, Dr. Ulrich Wolf, Im Grün 7 b, 7750 Konstanz 16, Federal Republic of Germany, declare that I am conversant with the German and English languages and that to the best of my knowledge and belief the accompanying document is a true translation of the text on which the European Patent Office intends to or has granted European Patent No. 0166287 in the name of Byk Gulden Lomberg Chemische Fabrik GmbH, Byk-Gulden-Str. 2, D-7750 Konstanz, Federal Republic of Germany.

Signed this 31th day of August 1989

Ulrich Wolf

.....

Dr. Ulrich Wolf

VERIFIED TRANSLATION OF THE
SPECIFICATION OF EUROPEAN PATENT

0 166 287

"Dialkoxypyridines, process for their preparation, their application and medicaments containing them"

BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH

FOR USE IN VALIDATING THE PATENT
IN THE UNITED KINGDOM

Field of application of the invention

The invention relates to new dialkoxypyridines, processes for their preparation, their use and medicaments containing them. The compounds according to the invention are used in the pharmaceutical industry as intermediates and for the preparation of medicaments.

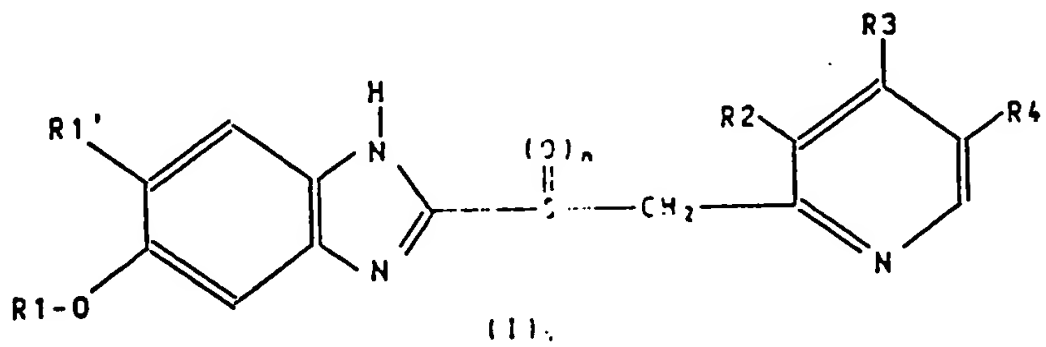
Prior art

European Patent Application 0,005,129 describes substituted pyridylsulfinylbenzimidazoles which are said to have properties of inhibiting the secretion of gastric acid. - The use of a number of benzimidazole derivatives for inhibiting the secretion of gastric acid is described in European Patent Application 0,074,341. British Patent Application GB 2,082,580 describes tricyclic imidazole derivatives which are said to inhibit the secretion of gastric acid and prevent the formation of ulcers.

It has now been found, surprisingly, that the dialkoxypyridines described below in more detail have interesting and unexpected properties in which they differ from the known compounds in an advantageous manner.

Description of the invention

The invention relates to new dialkoxypyridines of the general formula I



(I),

wherein

R1 represents a 1-3C-alkyl radical which is completely or predominantly substituted by fluorine,

or a chlorodifluoromethyl radical and
R1' repr sents a hydrogen atom or a halogen atom, trifluoromethyl, a 1-3C-alkyl radical, or a 1-3C-alkoxy radical which is optionally completely or predominantly substituted by fluorine, or
R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is optionally completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,
R3 represents a 1-3C-alkoxy radical
one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and
n represents the numbers 0 or 1,
and the salts of these compounds.

Examples which may be mentioned of 1-3C-alkyl radicals which are completely or predominantly substituted by fluorine are the 1,1,2-trifluoroethyl radical, the perfluoropropyl radical, the perfluoroethyl radical and, in particular, the 1,1,2,2-tetrafluoroethyl radical, the trifluoromethyl radical, the 2,2,2-trifluoroethyl radical and the difluoromethyl radical.

A halogen atom in the context of the present invention is a bromine, chlorine and, in particular, fluorine atom.

1-3C-Alkyl radicals are the propyl, isopropyl, ethyl and, in particular, methyl radical.

1-3C-Alkoxy radicals contain, in addition to the oxygen atom, the abovementioned 1-3C-alkyl radicals. The methoxy radical is preferred.

1-3C-Alkoxy radicals which are completely or predominantly substituted by fluorine contain, in addition to the oxygen atom, the abovementioned 1-3C-alkyl radicals which are completely or predominantly substituted by fluorine. Examples which may be mentioned are the 1,1,2,2-tetrafluoroethoxy, the trifluoromethoxy, the 2,2,2-trifluoroethoxy and the difluoromethoxy radical.

Examples which may be mentioned of 1-2C-alkylene-

dioxy radicals which are optionally completely or partly substituted by fluorine are the 1,1-difluoroethylenedioxy radical ($-O-CF_2-CH_2-O-$), the 1,1,2,2-tetrafluoroethylenedioxy radical ($-O-CF_2-CF_2-O-$), the 1,1,2-trifluoroethylenedioxy radical ($-O-CF_2-CHF-O-$) and, in particular, the difluoromethylenedioxy radical ($-O-CF_2-O-$), as substituted radicals, and the ethylenedioxy radical and the methylenedioxy radical, as unsubstituted radicals.

Preferred possible salts of compounds of the general formula I in which n denotes the number 0 (sulfides) are all the acid addition salts. Salts which may be mentioned in particular are the pharmacologically acceptable salts of the inorganic and organic acids usually employed in galenics. Pharmacologically unacceptable salts which may initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically acceptable salts by processes which are known to the expert. Examples of such suitable salts are water-soluble and water-insoluble acid addition salts, such as the hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate, citrate, gluconate, benzoate, hibenzate, fendizoate, butyrate, sulfosalicylate, maleate, laurate, malate, fumarate, succinate, oxalate, tartrate, amsonate, embonate, metembonate, stearate, tosylate, 2-hydroxy-3-naphthoate, 3-hydroxy-2-naphthoate or mesylate.

Preferred possible salts of compound of the general formula I in which n denotes the number 1 (sulfoxides) are basic salts, in particular pharmacologically acceptable salts with the inorganic and organic bases usually employed in galenics. Examples which may be mentioned of basic salts are the sodium, potassium, calcium or aluminum salts.

One embodiment (embodiment a) of the invention comprises compounds of the general formula I wherein R1' represents a hydrogen atom and R1, R2, R3, R4 and n have the

abovementioned meanings, and their salts.

Another mbodiment (embodiment b) of the invention comprises compounds of the general formula I wherein R1' represents a halogen atom, trifluoromethyl, a 1-3C-alkyl radical or a 1-4C-alkoxy radical which is optionally completely or predominantly substituted by fluorine and R1, R2, R3, R4 and n have the abovementioned meanings, and their salts.

Another embodiment (embodiment c) of the invention comprises compounds of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical and R2, R3, R4 and n have the abovementioned meanings, and their salts.

Another embodiment (embodiment d) of the invention comprises compounds of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is completely or partly substituted by fluorine and R2, R3, R4 and n have the abovementioned meanings, and their salts.

Another embodiment (embodiment e) of the invention comprises compounds of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a chlorotrifluoroethylenedioxy radical and R2, R3, R4 and n have the abovementioned meanings, and their salts.

Preferred compounds of embodiment a are those of the general formula I wherein R1 represents 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl or chlorodifluoromethyl, R1' represents a hydrogen atom, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom r methyl and n represents the numbers 0 or 1, and the salts of th se compounds.

Preferred compounds of embodiment b are those of the general formula I wherein R1 repr sents difluoromethyl, R1' represents difluoromethoxy or methoxy, R3 represents

methoxy, one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and n represents the numbers 0 or 1, and the salts of these compounds.

Preferred compounds of embodiment c are those of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a methylenedioxy or ethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents hydrogen or methyl and n represents the numbers 0 or 1, and the salts of these compounds.

Preferred compounds of embodiment d are those of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a difluoromethylenedioxy radical or a 1,1,2-trifluoroethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and n represents the numbers 0 or 1, and the salts of these compounds.

Preferred compounds of embodiment e are those of the general formula I wherein R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a chlorotrifluoroethylenedioxy radical, R3 represents methoxy, one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and n represents the numbers 0 or 1, and the salts of these compounds.

Examples which may be mentioned of compounds according to the invention are: 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole,

5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5,6-bis (difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole, 2-[(3,4-dimethoxy-5-methyl-2-pyridyl) methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole,

2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole, 2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)-methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole,

5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 2,2-difluoro-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 2,2-difluoro-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(4,5-diethoxy-3-methyl-2-pyridyl)-methylthio]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(4,5-diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]-benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(4,5-diethoxy-2-pyridyl)-methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino-[2,3-f]benzimidazole, 2-[(4,5-diethoxy-2-pyridyl)methyl-sulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino-[2,3-f]benzimidazole, 2-[(4,5-diethoxy-3-methyl-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(4,5-diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-

[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2,2-difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 2,2-difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazole, 2,2-difluoro-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 2,2-difluoro-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(3,4-diethoxy-5-methyl-2-pyridyl)methylthio]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(3,4-diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole,

6,6,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(3,4-diethoxy-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(3,4-diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(3,4-diethoxy-5-methyl-2-pyridyl)methylthio]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 2-[(3,4-diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6-difluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]-benzimidazole, 6,6,7,7-tetrafluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]-benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(3,4-di-methoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]-benzimidazole, 6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-

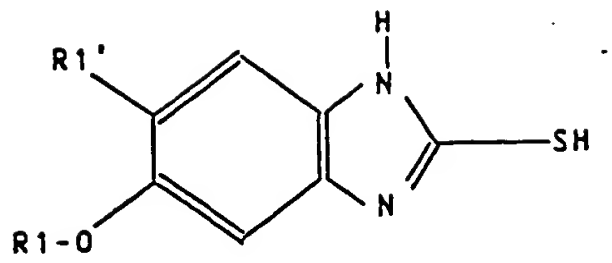
[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dixolo[4,5-f]benzimidazole, 6-[(3,4-dimethoxy-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole, 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, and the salts of these compounds.

Due to the tautomerism in the imidazole ring, 5-substitution in the benzimidazole is identical to 6-substitution. Accordingly, in the compounds in which R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a substituted ethylenedioxy radical, the 6-position in the [1,4]-dioxino[2,3-f]-benzimidazole part is identical to the 7-position.

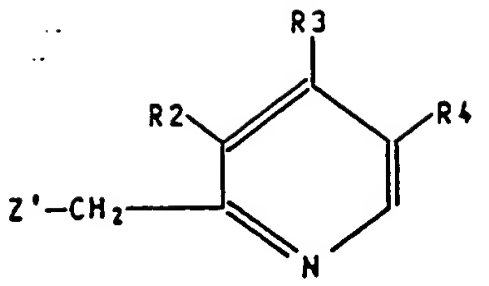
The invention furthermore relates to a process for the preparation of the dialkoxypyridines of the general formula I wherein R1, R1', R2, R3, R4 and n have the abovementioned meanings, and their salts.

The process is characterized in that

a) mercaptobenzimidazoles of the general formula II are reacted with picoline derivatives III



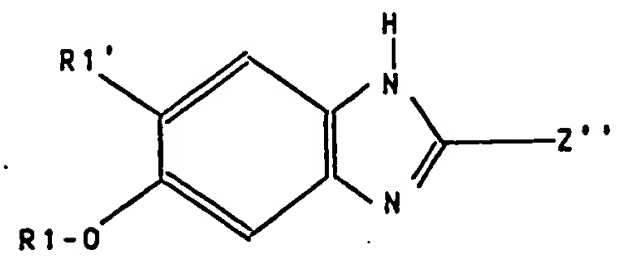
(II)



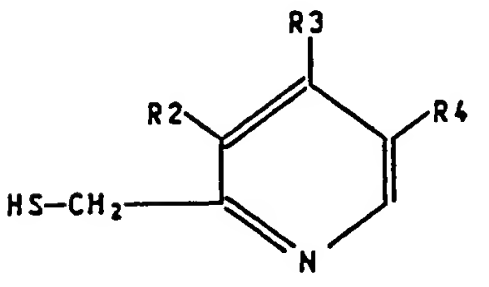
(III),

or

b) benzimidazoles of the general formula IV are reacted with mercaptopicolines V



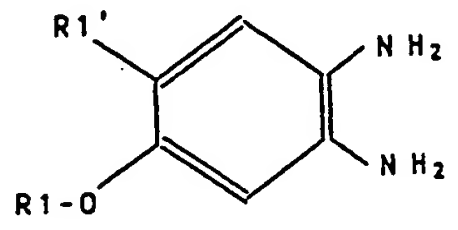
(IV)



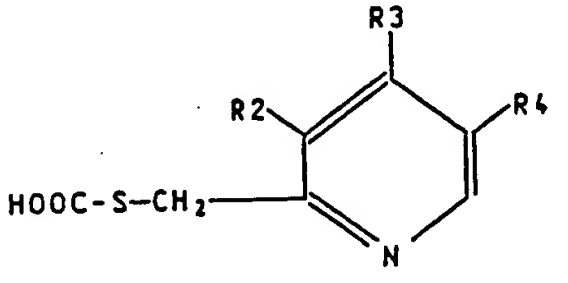
(V),

or

c) o-phenylenediamines of the general formula VI are reacted with formic acid derivatives VII

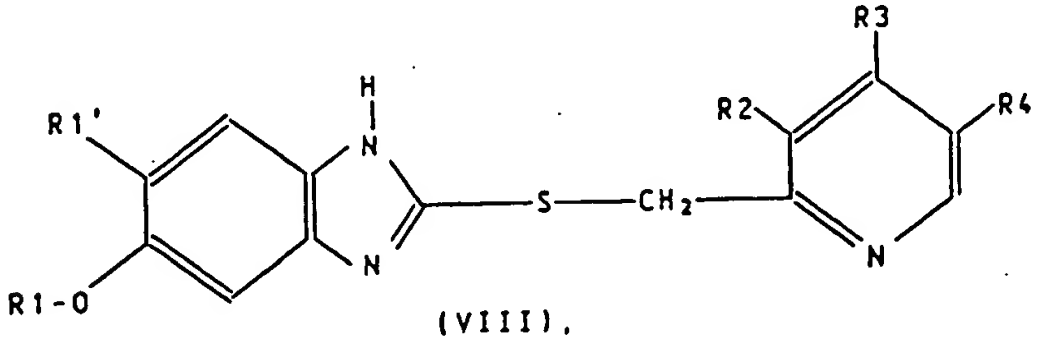


(VI)



(VII),

and, if appropriate, the 2-benzimidazolyl 2-pyridylmethyl sulfides of the general formula VIII obtained according to a), b) or c)

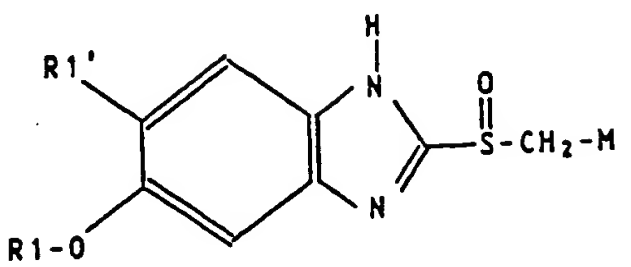


(VIII),

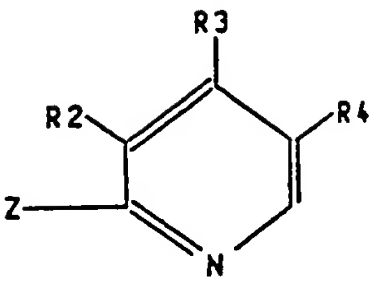
are then oxidized and/or converted into th salts,

or in that

d) benzimidazoles of the general formula IX are reacted with pyridine derivativex X



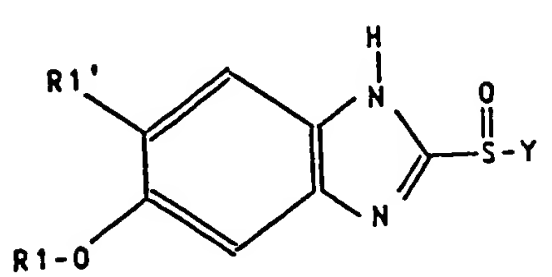
(IX)



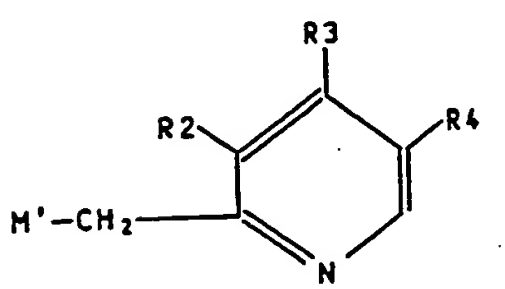
(X),

or

e) sulfinyl derivatives of the general formula XI are reacted with 2-picoline derivatives XII



(XI)



(XII),

and, if appropriate, the products are then converted into the salts, Y, Z, Z' and Z'' representing suitable leaving groups, M representing an alkali metal atom (Li, Na or K), M' representing the equivalent of a metal atom and R1, R1', R2, R3, R4 and n having the abovementioned meanings.

The compounds II-XII can be employed in the above-mentioned reactions as such or, if appropriate, in the form of their salts.

Preparation processes a), b) and c) lead to the sulfides according to the invention, and the oxidation of the compounds VIII and processes d) and e) give the sulfoxides according to the invention.

The expert is familiar, on the basis of his expert knowledge, with what leaving groups Y, Z, Z' and Z'' are suitable. A suitable leaving group Y is, for example, a group which forms a reactive sulfinic acid derivative together with the sulfinyl group to which it is bonded. Examples which may be mentioned of suitable

leaving groups Y are alkoxy, dialkylamino and alkylmercapto groups. Examples which may be mentioned of suitable leaving groups Z, Z' or Z'' are halogen atoms, in particular chlorine atoms, or hydroxyl groups activated by esterification (for example with p-toluenesulfonic acid). The equivalent of a metal atom M' is, for example, an alkali metal atom (Li, Na or K), or an alkaline earth metal atom (for example Mg), which is substituted by a halogen atom (for example Br, Grignard reagent), or any other optionally substituted metal atom which is known to react like the abovementioned metals in replacement reactions of organometallic compounds.

The reaction of II with III is carried out in a manner which is known per se in suitable solvents, preferably polar protic or aprotic solvents (such as methanol, isopropanol, dimethyl sulfoxide, acetone, dimethylformamide or acetonitrile) with the addition of or exclusion of water. It is carried out, for example, in the presence of a proton acceptor. Suitable proton acceptors are alkali metal hydroxides, such as sodium hydroxide, alkali metal carbonates, such as potassium carbonate, or tertiary amines, such as pyridine, triethylamine or ethyldiisopropylamine. Alternatively, the reaction can also be carried out without a proton acceptor, in which case - depending on the nature of the starting compounds - the acid addition salts can first be separated off, if appropriate, in a particularly pure form. The reaction temperature can be between 0° and 150°C, temperatures between 20° and 80°C being preferred in the presence of proton acceptors and temperatures between 60° and 120°C - in particular the boiling point of the solvent used - being preferred without proton acceptors. The reaction times are between 0.5 and 24 hours.

Similar reaction conditions to those in the reaction of II with III can be used in the reaction of IV with V, which is carried out in a manner which is known per se.

The reaction of VI with VII is preferably carried

out in polar, optionally water-containing solvents in the presence of a strong acid, for example hydrochloric acid, in particular at the boiling point of the solvent used.

The oxidation of the sulfides VIII is carried out in a manner which is known per se under conditions such as those familiar to the expert for the oxidation of sulfides to sulfoxides [in this context, see, for example, J. Drabowicz and M. Mikolajczyk, Organic preparations and procedures int. 14(1-2), 45-89 (1982) or E. Block in S. Patai, The Chemistry of Functional Groups, Supplement E. Part 1, pages 539-608, John Wiley and Sons (Interscience Publication), 1980]. Possible oxidizing agents are all the reagents usually employed for the oxidation of sulfides to sulfoxides, for example hypohalites, and in particular peroxyacids, such as, for example, peroxyacetic acid, trifluoroperoxyacetic acid, 3,5-dinitroperoxybenzoic acid, peroxymaleic acid or, preferably, m-chloroperoxybenzoic acid.

The reaction temperature is between -70°C and the boiling point of the solvent used (depending on the reactivity of the oxidizing agent and the solvent used, but preferably between -50° and +20°C. The oxidation is advantageously carried out in inert solvents, for example aromatic or chlorinated hydrocarbons, such as benzene, toluene, dichloromethane or chloroform, or in esters, such as ethyl acetate or isopropyl acetate, or in ethers, such as dioxane, with the addition of water or without water.

The reaction of IX with X is preferably carried out in inert solvents such as are also usually employed for the reaction of enolate ions with alkylating agents. Examples which may be mentioned are aromatic solvents, such as benzene or toluene. The reaction temperature is as a rule between 0° and 120°C (depending on the nature of the alkali metal atom M and the leaving group Z), the boiling point of the solvent used being preferred. For example [if M represents Li(lithium) and Z represents Cl(chlorine) and the reaction is carried out in benzene],

the boiling point of benzene (80°C) is preferred.

The compounds XI are reacted with the compounds XII in a manner which is known per se, such as is familiar to the expert for the reaction of organometallic compounds.

Depending on the nature of the starting compounds, which can optionally also be employed in the form of their salts, and depending on the reaction conditions, the compounds according to the invention are initially obtained either as such or in the form of their salts.

The salts are moreover obtained by dissolving the free compounds in a suitable solvent, for example in a chlorinated hydrocarbon, such as methylene chloride or chloroform, a low-molecular weight aliphatic alcohol (ethanol or isopropanol), an ether (diisopropyl ether), a ketone (acetone) or water, which contains the desired acid or base, or to which the desired acid or base - if appropriate in the exactly calculated stoichiometric amount - is then added.

The salts are obtained by filtration, reprecipitation, precipitation or by evaporation of the solvent.

The salts obtained can be converted into the free compounds by alkalization or acidification, for example with aqueous sodium bicarbonate or with dilute hydrochloric acid, and these can in turn be converted into the salts. In this manner, the compounds can be purified, or pharmacologically unacceptable salts can be converted into pharmacologically acceptable salts.

The sulfoxides according to the invention are optically active compounds. The invention therefore relates both to the enantiomers and to their mixtures and racemates. The enantiomers can be separated in a manner which is known per se (for example by preparation and separation of corresponding diastereoisomeric compounds). However, the enantiomers can also be prepared by asymmetric synthesis, for example by reaction of optically active pure compounds XI or diastereoisomeric pure compounds XI with compounds XII [in this context, see

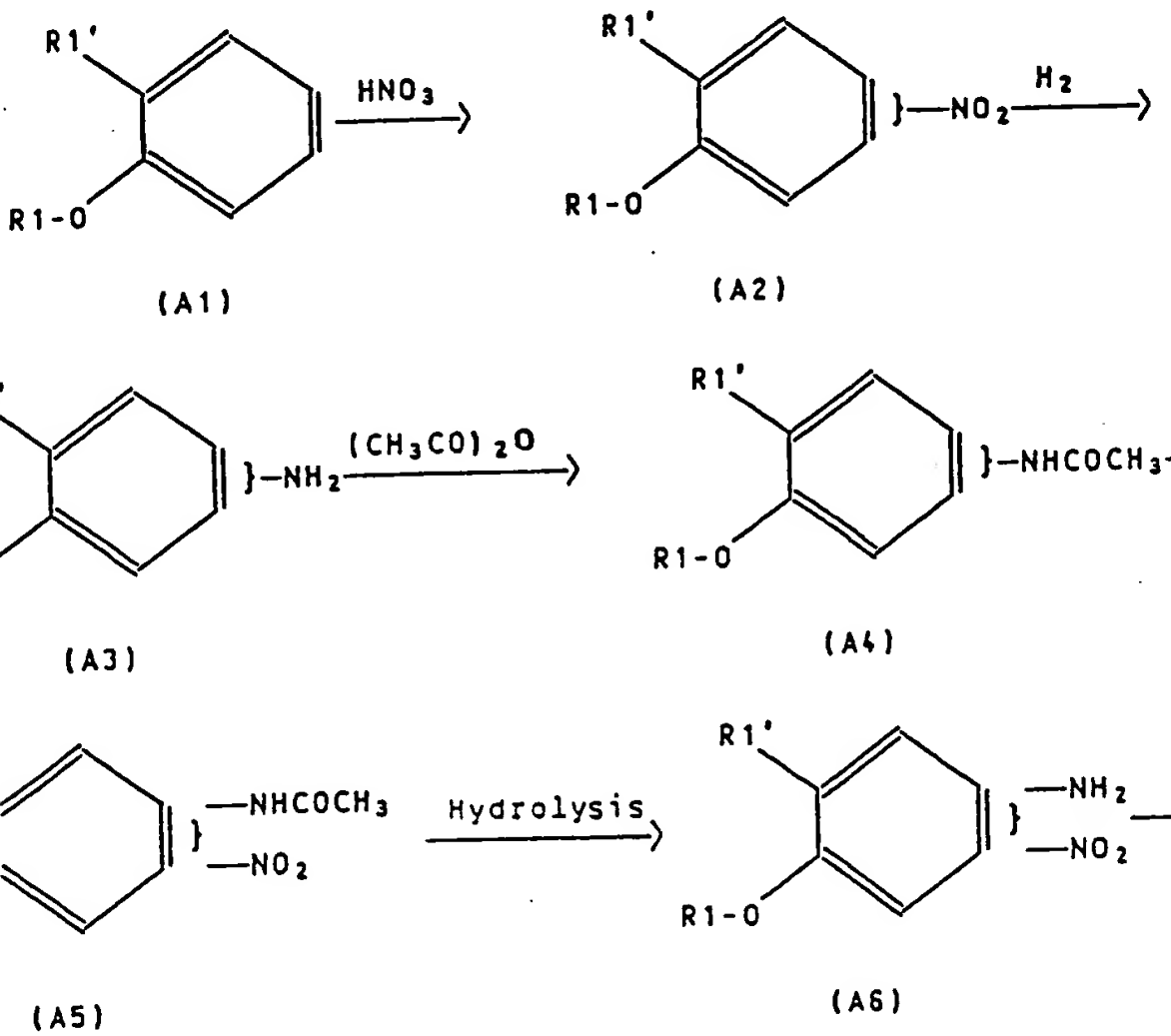
K.K. Andersen, Tetrahedron Lett., 93 (1962)].

The compounds according to the invention are preferably synthesized by reaction of II with III and, if appropriate, subsequent oxidation of the sulfide VIII formed.

The compounds of the general formula II are known in some cases (German Offenlegungsschrift 3,132,613), or they can be prepared analogously to known instructions. Compounds II are obtained, for example, by reacting compounds VI with carbon disulfide in the presence of alkali metal hydroxides or with alkali metal O-ethyl dithiocarbonates.

The compounds VI can be synthesized by the general preparation methods described in the following equation A:

Equation A:



The starting compounds A1 - A3 can be prepared by known methods or by methods analogous to these [for example J.Org.Chem. 44, 2907-2910 (1979); J.Org.Chem. 29, 1-11 (1964); German Offenlegungsschrift 2,029,556; German

Offenlegungsschrift 2,848,531; J.Fluorine Chem. 18, 281-91 (1981); and Synthesis 1980, 727-8], it also being possible for isomer mixtures to be formed in the case of non-identical substituents R1' and R1-O-.

The compounds IV, IX and XI can be prepared, for example, from the compounds II in a manner known to the expert.

The compounds IX are obtained, for example, from the compounds II by methylation, oxidation and subsequent deprotonation - for example with alkali metal hydrides or alcoholates or customary organometallic compounds. The compounds X are prepared in accordance with the method of Z. Talik, Roczniki Chem. 35, 475 (1961).

The compounds III can be prepared - depending on their substitution pattern - in various ways:

1. **Compounds III where R2 and R3 = 1-3C-alkoxy and R4 = a hydrogen atom or 1-3C-alkyl.**

These compounds are prepared, for example, starting from 3-hydroxy- or 3-hydroxy-5-alkyl-pyridines which are known or can be prepared by a known route, by benzylation of the hydroxyl group (for example with potassium hydroxide and benzyl chloride in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitrating acid), replacement of the nitro group by the 1-3C-alkoxy group (for example by reaction with alkali metal alkoxide), reductive debenzylation and simultaneous N-deoxygenation (for example with hydrogen over palladium-on-charcoal in an acid medium), introduction of the hydroxymethyl group in the o-position relative to the pyridine nitrogen (for example by reaction with alkaline formalin solution), conversion of the 3-hydroxy group into a 1-3C-alkoxy group (for example by alkylation with 1-3C-alkyl iodide in a basic medium) and introduction of the leaving group Z' (for example by reaction with thionyl chloride). In a preferred alternative, the compounds are prepared starting from 3-hydroxy-2-alkyl- or

3-hydroxy-2,5-dialkyl-pyridines, which are known or can be prepared by a known route, by alkylation of the hydroxyl group (for example with potassium hydroxide and methyl iodide in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitric acid), replacement of the nitro group by the 1-3C-alkoxy group (for example by reaction with alkali metal alkoxide), conversion into the 2-acetoxymethylpyridine (for example with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

2. Compounds III where R3 and R4 = 1-3C-alkoxy and R2 = a hydrogen atom.

These compounds are prepared, for example, starting from known 5-hydroxy-2-methylpyridines by alkylation of the hydroxyl group (for example with 1-3C-alkyl iodide and potassium hydroxide in dimethyl sulfoxide), N-oxidation (for example with 30% strength hydrogen peroxide), nitration in the 4-position (for example with nitrating acid), replacement of the nitro group by the 1-3C-alkoxy group (for example by reaction with alkali metal alkoxide), conversion into the 2-acetoxymethylpyridine (for example with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the 2-hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

3. Compounds III where R3 and R4 = 1-3C-alkoxy and R2 = 1-3C-alkyl.

These compounds are prepared, for example, starting from 2-methyl-3-alkyl-4-alkoxypyridines which are known or can be prepared by a known route (see, for example, European Patent A-0,080,602), by N-oxidation (for example with 30% strength hydrogen peroxide), controlled acetoxylation and subsequent hydrolysis in the 5-position (for example with acetic anhydride and subsequently sodium hydroxide solution), alkylation of the

5-hydroxy group (for example with 1-3C-alkyl iodide and sodium hydroxide solution in dimethyl sulfoxide), N-oxidation (for example with m-chloroperoxybenzoic acid), conversion into the 2-acetoxymethylpyridine (for xample with hot acetic anhydride), hydrolysis (for example with dilute sodium hydroxide solution) to the 2-hydroxymethyl group and introduction of the leaving group Z' (for example by reaction with thionyl chloride).

The specific reaction conditions (temperatures, reaction times, solvents and the like) in the synthesis routes outlined above for the preparation of the compounds III which are necessary are familiar to the expert on the basis of his expert knowledge. Precise preparation of individual representatives of the compounds III is described in the examples. Other representatives are prepared analogously.

The compounds of the general formula III, wherein R3 represents a 1-3C-alkoxy radical, one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a 1-3C-alkyl radical are new and are likewise the subject of the invention.

The compounds V, VII and XII are prepared, for example, starting from the compounds III by routes known to the expert.

The following examples illustrate the invention in more detail without limiting it. The invention preferably relates to the compounds of the general formula I listed by name in the examples and salts of these compounds. In the examples, m.p. denotes melting point, decomp. represents decomposition and b.p. represents boiling point.

Examples

1. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole

1.57 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride are added to a solution of 1.64 g of 2-mercapto-5-trifluoromethoxy-1H-benzimidazole in 40 ml of ethanol and 20 ml of 1N sodium hydroxide solution, the mixture is stirred at 20°C for 2 hours and then at 40°C for a further hour, the ethanol is distilled off on a rotary evaporator (1kPa/40°C) and the colorless precipitate which thereby separates out is filtered off over a suction filter, rinsed with 1N sodium hydroxide solution and water and dried. 2.15 g (79% of theory) of the title

compound of m.p. 92-93°C are obtained.

5-Chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (oil) 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (m.p. 159-160°C) and 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole are obtained analogously by reacting 5-chlorodifluoromethoxy-2-mercato-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-mercapto-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole with 2-chloromethyl-4,5-dimethoxypyridinium chloride.

2. <u>2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole</u>

5.5 ml of a 0.2M solution of m-chloroperoxybenzoic acid in methylene chloride are added dropwise to a solution of 0.36 g of 2-[4,5-dimethoxy-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole in 10 ml of methylene chloride at -50°C and the mixture is stirred at the stated temperature for a further 30 minutes. After addition of 0.3 ml of triethylamine, the cold reaction mixture is stirred into 10 ml of 5% strength sodium thiosulfate solution and 10 ml of 5% strength sodium carbonate solution, after phase separation three further extractions with 10 ml of methylene chloride are performed, the combined organic phases are washed once with 5 ml of 5% strength sodium thiosulfate solution and dried, the drying agent (magnesium sulfate) is filtered off and the filtrate is concentrated. The residue is made to crystallize with diisopropyl ether and is then reprecipitated from methylene chloride/diisopropyl ether. 0.27 g (72% of theory) of the title compound is obtained as a colorless solid of m.p. 159-61°C (decomp.).

5-Chlorodifluoromethoxy-2-[(4,5-dimethoxy-2-

pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 159°C (decomp.)], 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H- benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2,2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole are obtained analogously by oxidation of other sulfides of Example 1 with m-chloroperoxybenzoic acid.

3. <u>2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole</u>

1.40 g of the title compound are obtained as a yellow oil by the procedure described in Example 1, by reacting 1.07 g of 2-mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 0.90 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 15 ml of ethanol with the addition of 17 ml of 0.5 N sodium hydroxide solution. Recrystallization from petroleum ether gives the product in the form of colorless crystals of m.p. 125-127°C.

Yield: 1.20 g (72% of theory).

4. <u>2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole</u>

A solution of the product in methylene chloride is obtained by the procedure described in Example 2 by oxidation of 0.76 g of 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 19 ml of a 0.1 M solution of m-chloroperoxybenzoic acid in 30 ml of methylene chloride at -40°C, after extraction. After drying the solution over magnesium sulfate, the drying agent is filtered off, the filtrate is concentrated and the residue is crystallized from methylene chloride/diisopropyl ether. 0.64 g (82% of theory) of the title compound is obtained in the form of colorless crystals of m.p. 160-162°C (decomp.).

5. <u>2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole</u>

1.0 g of 2-mercapto-5-(2,2,2-trifluoroethoxy)-1H-

benzimidazole are dissolved in 15 ml of ethanol and 8.5 ml of 1N sodium hydroxide solution, 0.90 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride are added and the mixture is stirred for 20 hours. After addition of 30 ml of water, the mixture is extracted three times with 30 ml of methylene chloride each time, the methylene chloride phase is washed once with 5 ml of 0.1 N sodium hydroxide solution, the combined organic phases are dried over magnesium sulfate and, after the drying agent has been filtered off, the filtrate is completely concentrated. 1.51 g (94% of theory) of the title compound are obtained as an amorphous solid residue of m.p. 55-57°C.

6. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole

0.8 g of 2-[(4,5-dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole is dissolved in 15 ml of dioxane and 2.5 ml of 1 N sodium hydroxide solution. A mixture of 3 ml of 8 percent strength sodium hypochlorite solution and 3.5 ml of 1N sodium hydroxide solution are added dropwise in the course of 2 hours, while cooling to 0-5°C. After addition of 5 ml of 5% strength sodium thiosulfate solution, the mixture is concentrated to dryness, the residue is taken up in water and the mixture is brought to pH 7 with phosphate buffer. The solid which has precipitated out is filtered off with suction, dried and recrystallized from ethyl acetate/diisopropyl ether. 0.45 g (55% of theory) of the title compound is obtained as colorless crystals of m.p. 142-143°C (decomp.).

7. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

1.46 g (83% of theory) of the tital compound of m.p. 127-128°C (colorless powder) are obtained by the procedure described in Example 1 by reaction of 1.07 g of 2-mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 0.96 g of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 12 ml of ethanol, with the addition of 17 ml of 0.5 N sodium hydroxide solution.

8. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

0.8 g of a pale yellow oil is obtained by the procedure described in Example 2 by oxidation of 0.99 g of 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole with 12 ml of a 0.2 M solution of m-chloroperoxybenzoic acid in methylene chloride at -40°C for a reaction time of 1.5 hours. Recrystallization twice from methylene chloride/diisopropyl ether gives 0.30 g (34% of theory) of the title compound in the form of colorless crystals of m.p. 125°C (decomp.).

9. 5-Difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole

0.64 g (84% of theory) of the title compound of m.p. 100-102°C (colorless crystalline powder) is obtained by the procedure described in Example 1 by reaction of 0.38 g (2 mmol) of 5-difluoromethoxy-2-mercapto-1H-benzimidazole with 0.48 g (2 mmol) of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 10 ml of ethanol, with the addition of 8.8 ml of 1N sodium hydroxide solution, after two hours at 50°C.

10. 2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

0.38 g (1.7 mmol) of 2-chloromethyl-3,4-dimethoxy-pyridinium chloride is added to a solution of 0.46 g (1.7 mmol) of 2-mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole in 10 ml of ethanol, 10 ml of water and 1.8 ml of 2N sodium hydroxide solution; after the mixture has been stirred at 20°C for one hour, a further 10 ml of water are added dropwise; the mixture is then stirred at 20°C for a further four hours. The solid which has precipitated out is filtered off, washed with 0.01 N sodium hydroxide solution and then with water until neutral and dried to constant weight. 0.63 g (90% of theory) of the title compound is obtained as a colorless crystalline powder of m.p. 98-102°C.

5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole (m.p. 104-108°C) and 5-difluorom thoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)-methylthio]-1H-benzimidazole (m.p. 137-138°C) are obtained analogously by reacting 5-difluoromethoxy-2-mercapto-1H-benzimidazole and 5-difluoromethoxy-6-methoxy-2-mercapto-1H-benzimidazole with 2-chloromethyl-3,4-dimethoxypyridinium chloride.

11. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole

1.40 g (70% of theory) of the title compound are obtained by the procedure described in Example 1 by reaction of 1.15 g of 2-mercapto-5-trifluoromethoxy-1H-benzimidazole with 1.20 g of 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride in 20 ml of isopropanol, with the addition of 20.5 ml of 0.5N sodium hydroxide solution. Recrystallization from diisopropyl ether/petroleum ether gives a product of m.p. 94-97°C.

2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazole are obtained analogously by reacting 2-mercapto-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-chlorodifluoromethoxy-2-mercapto-1H-benzimidazole, 5,6-bis(difluoromethoxy)-2-mercapto-1H-benzimidazole, 5-difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole and 5-difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole with 2-chloromethyl-4,5-dimethoxy-3-methyl-pyridinium chloride.

12. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole

0.19 g (76% of theory) of the title compound is obtained as a colorless powder by the procedure described in Example 2 by oxidation of 0.24 g of 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluoromethoxy-1H-benzimidazole with 3.3 ml of a 0.2 M solution of m-chloroperoxybenzoic acid in methylene chloride at -50°C and reprecipitation from methylene chloride/diisopropyl ether; 158-159°C decomp.

2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole, 5-

chlorodifluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 133-135°C (decomp.)], 5,6-bis(difluoromethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 5-difluoromethoxy-6-fluoro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole, 2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole [m.p. 117-119°C (decomp.)] and 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole [m.p. 136° (decomp.)] are obtained analogously by oxidation of the sulfides of the above Examples 9 to 11 with m-chloroperoxybenzoic acid.

13. 2,2-Difluoro-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.96 g of 2-chloromethyl-4,5-dimethoxy-3-methyl-pyridinium chloride are added to a solution of 0.92 g of 2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol in 10 ml of ethanol and 10 ml of 1N sodium hydroxide solution. The yellow reaction mixture is stirred at 20°C for 1 hour, a further 10 ml of water are added, whereupon a colorless solid precipitates out, the mixture is stirred for a further 5 hours and filtered and the residue is rinsed with 1N sodium hydroxide solution and water and dried to constant weight. The amorphous powder is recrystallized from methylene chloride/diisopropyl ether. 1.5 g (93% of theory) of the title compound are obtained in the form of colorless crystals of m.p. 160-61°C.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]-benzimidazole are obtained analogously by reacting 6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-

2-thiol, 6-chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol or 6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol with 2-chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride.

14. 2,2-Difluoro-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

21 ml of a 0.1N solution of m-chloroperoxybenzoic acid in methylene chloride are added dropwise to a suspension, cooled to -40°C, of 0.80 g of 2,2-difluoro-6[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole in 10 ml of methylene chloride in the course of 10 minutes. The mixture is stirred for a further 20 minutes, during which the temperature is allowed to rise to -20°C, and 0.5 ml of triethylamine are added and the reaction mixture is poured into 40 ml of in each case 5% strength sodium thiosulfate solution and 5% strength sodium carbonate solution. After phase separation, the aqueous phase is extracted twice more with 20 ml of methylene chloride each time; the combined organic phases are washed with a mixture of in each case 5 ml of sodium thiosulfate solution and sodium carbonate solution, dried and concentrated. The residue is recrystallized from methylene chloride/diisopropyl ether. 0.62 g (75% of theory) of the title compound is obtained; decomp. 189-90°C.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]-benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole are obtained analogously by oxidation of the other sulfides mentioned under Example 13 with m-chloroperoxybenzoic acid.

15. 6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

A brownish solid is obtained by the procedur described in Example 13 by reaction of 0.85 g of 5H-

[1,3]-dioxolo[4,5-f]-benzimidazole-6-thiol with 0.98 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 10 ml of ethanol and 10 ml of water, with the addition of 8.5 ml of 1N sodium hydroxide solution, after a reaction time of 20 hours and after concentration by removing the solvent in vacuo, to a volume of 10 ml. The crude product is dissolved in 30 ml of methylene chloride, the solution is clarified with active earth (for example Tonsil®) and concentrated, the residue is crystallized by addition of diisopropyl ether and the now pale yellow solid is boiled up in 5 ml of methanol. 0.90 g (60% of theory) of the title compound is obtained as a colorless solid of m.p. 198-200°C.

16. 6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazole

0.27 g of the title compound in the form of colorless crystals of m.p. 199°C (decomp.) is obtained by the procedure described in Example 14 by oxidation of 0.7 g of 6-[4,5-dimethoxy-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole with 23 ml of a 0.1 M solution of m-chloroperoxybenzoic acid, after recrystallization from diethyl ether.

17. 2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

1.05 g (92% of theory) of the title compound are obtained as a finely crystalline, colorless powder of m.p. 185-187°C by the procedure described in Example 13 by reaction of 0,69 g (3 mmol) of 2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol with 0,67 g (3 mmol) of 2-chloromethyl-3,4-dimethoxypyridinium chloride in a mixture of 10 ml of ethanol and 10 ml of water, with the addition of 3.3 ml of 2N sodium hydroxide solution, after a reaction time of 10 hours. 6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole (m.p. 155-157°C) is obtained analogously by reacting 5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol with 2-chloromethyl-3,4-dimethoxypyridinium chlorid .

18. 6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.78 g (4 mmol) of 5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol is heat d at the boiling point under reflux with 0.95 g (4 mmol) of

2-chlor methyl-4,5-dimethoxy-3-m thyl-pyridinium chloride in 30 ml of isopropanol for 15 hours. The solid which has precipitated out is filtered off and extracted by stirring with isopropanol, the mixture is filtered again and the residue is dried to constant weight. 1.0 g (59% of theory) of the dihydrochloride of the title compound is obtained as a colorless solid of m.p. 206°C (decomp.).

19. 2,2-Difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

6.3 ml of 1N sodium hydroxide solution are added dropwise to a solution, warmed to 50°C, of 0.69 g of 2,2-difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol and 0.67 g of 2-chloromethyl-4,5-dimethoxypyridinium chloride in 9 ml of ethanol and 4 ml of water in the course of one minute. On cooling the clear reaction mixture to 20°C a colorless precipitate separates out after a short time. The mixture is stirred at 20°C for a further 5 hours and the precipitate is filtered off with suction over a suction filter, rinsed with 1N sodium hydroxide solution and water and dried to constant weight. The beige solid is dissolved in 10 ml of methylene chloride, insoluble constituents are filtered off, the filtrate is concentrated and the residue is made to crystallize by addition of diisopropyl ether and after cooling. 1.02 g (90% of theory) of the title compound of m.p. 189-91°C are obtained.

6,6,7-Trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazole are obtained analogously by reacting 6,6,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol, 6-chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol or 6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol with 2-chloromethyl-4,5-dimethoxy-pyridinium chloride.

20. 2,2-Difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole

0.76 g of 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole are dissolved in 10 ml of dioxane and 2 ml of 1N sodium hydroxide solution. An equimolar amount of a titrated aqueous sodium hypochlorite solution, to which 1 mole per liter of sodium hydroxide solution has been added, is first added dropwise, while cooling with ice, and after one hour a further equivalent and after 3 hours half the equimolar amount of sodium hypochlorite are added, to achieve complete reaction. After a reaction time of 4 hours, 5 ml of 5% strength sodium thiosulfate solution and another 25 ml of dioxane are added and the upper dioxane phase is separated off, washed once with 5 ml of sodium thiosulfate solution and concentrated on a rotary evaporator. The oily residue is dissolved in 20 ml of water and 10 ml of ethyl acetate and the solution is brought to pH 7 with about 100 ml of a buffer solution of pH 6.8. The solid which has precipitated out is filtered off with suction over a suction filter, washed with water, extracted by stirring at 0°C with acetone and dried. 0.7 g (87% of theory) of the title compound is obtained in the form of colorless crystals; decomp. at 211-213°C.

2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo [4,5-f]-benzimidazole [m.p. 177-178°C (decomp.)], 6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo [4,5-f]-benzimidazole, 6,6,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole, 6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole [m.p. 170-171°C (decomp.)], 6-chloro-6,7,7-trifluoro-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole and 6,7-dihydro-2-[(4,5-dimthoxy-2-pyridyl)mthylsulfinyl]-1H-[1,4]-dixino[2,3-f]benzimidazole are obtained analogously by oxidation of the other sulfides mentioned in Examples 17 to 19 with sodium hypochlorite solution.

21. 2-Mercapto-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

a) 55 g of 1-nitro-4-(1,1,2,2-tetrafluoroethoxy)-benzene are hydrogenated in 300 ml of ethanol over 0.5 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under atmospheric pressure at 20-45°C for 1 hour, the catalyst is filtered off and the solution is concentrated in vacuo at 40°C. The 4-(1,1,2,2-tetrafluoroethoxy)aniline is diluted with 100 ml of glacial acetic acid, 23 ml of acetic anhydride are added dropwise at room temperature, 2 ml of water are added after 30 minutes, the solution is concentrated at 50°C in vacuo after a short time and 500 ml of ice-water are added. 56 g (97%) of N-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-acetamide of m.p. 121-122°C are obtained.

b) 55 g of the above compound are dissolved in 380 ml of dichloromethane, 55 ml of 100% strength nitric acid are added dropwise at room temperature in the course of 10 minutes and the mixture is stirred for a further 6 hours. The organic solution is then washed with aqueous sodium carbonate solution and water, dried with magnesium sulfate and concentrated. 65 g (100%) of N-[2-nitro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]-acetamide of m.p. 80-81°C (from cyclohexane) are obtained.

c) 63 g of the above compound are dissolved in 450 ml of methanol, 106 ml of 6 M sodium hydroxide solution are added dropwise at room temperature, the mixture is cooled in an ice-bath and 53 g (98%) of 2-nitro-4-(1,1,2,2-tetrafluoroethoxy)-aniline (m.p. 85-86°C) are precipitated by dropwise addition of 900 ml of water.

d) 33 g of the above compound are hydrogenated in about 600 ml of isopropanol over 1 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under normal pressure at room temperature. The catalyst is filtered off with suction and 34 g (89%) of 4-(1,1,2,2-tetrafluoroethoxy)-1,2-phenylenediamine dihydrochloride of m.p. 275-276°C (decomposition) are

precipitated with 4 M hydrogen chloride in ether.

e) 330 ml of ethanol, 60 ml of water, 8.9 g of sodium hydroxide and 23 g of potassium O-ethyldithiocarbonate (recrystallized from isopropanol) are added to 33 g of the above compound and the mixture is heated at the boiling point under reflux for 15 hours. 1.2 l of ice-water are added, the pH is brought to 13-14 with sodium hydroxide solution and the mixture is clarified with active charcoal and precipitated with dilute hydrochloric acid to pH 3.5. 27 g (91%) of the title compound of m.p. 316-319°C (from isopropanol) are obtained.

22. 2-Mercapto-5-trifluoromethoxy-1H-benzimidazole

The title compound of m.p. 305-307°C (decomposition, from toluene) is obtained in 75% yield analogously to Example 21e) by reaction of 4-trifluoromethoxy-1,2-phenylenediamine dihydrochloride (compare C.A. 55, 23408d, 1961) with potassium O-ethyldithiocarbonate and sodium hydroxide solution in ethanol.

23. 2-Mercapto-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole

a) 50 g of 1-(2,2,2-trifluoroethoxy)-4-nitrobenzene (Synthesis 1980, page 727) are hydrogenated and acetylated analogously to Example 21a). 50 g (95%) of N-[4-(2,2,2-trifluoroethoxy)phenyl]acetamide (m.p. 140-141°C) are obtained.

b) 42 g of the above compound are stirred with 9.7 ml of 100% strength nitric acid in 290 ml of glacial acetic acid at room temperature for 18 hours and the mixture is precipitated with water. 47 g (94%) of N-[2-nitro-4-(2,2,2-trifluoroethoxy)phenyl]-acetamide (m.p. 117-118°C) are obtained.

c) 47 g of the above compound are hydrolyzed analogously to Example 21c to give 38.7 g (97%) of 2-nitro-4-(2,2,2-trifluoroethoxy)-aniline (m.p. 84-85°C).

d) 37 g of the above compound are hydrogenated analogously to Example 21d) to give 41 g (94%) of 4-(2,2,2-trifluoroethoxy)-1,2-phenylenediamine dihydrochloride of m.p. 230-233°C (decomposition).

e) 30 g (94%) of the title compound (m.p. 288-290°C)

are obtained analogously to Example 21e) from 36 g of the above compound.

24. 5-Chlorodifluoromethoxy-2-mercapto-1H-benzimidazole

a) 10.0 g of N-[4-(chlorodifluoromethoxy)phenyl]-acetamide (m.p. 101-103°C, from 4-chlorodifluoromethoxyaniline and acetic anhydride) and 12.3 ml of 100% strength nitric acid are stirred in 80 ml of dichloromethane at 20°C for 4 hours. The mixture is neutralized with aqueous potassium bicarbonate solution and the organic layer is concentrated to give 11.4 g (96%) of N-(4-chlorodifluoromethoxy-2-nitrophenyl)-acetamide (m.p. 89-91°C).

b) 8.6 ml of a 30% strength solution of sodium methylate in methanol are added dropwise to 10.5 g of the above compound in 200 ml of methanol at 5°C, the mixture is stirred for 2 hours, without cooling, ice-water is added and the pH is brought to 8 to give 8.7 g (97%) of 4-chlorodifluoromethoxy-2-nitroaniline (m.p. 40-42°C).

c) 8.5 g of the above compound are hydrogenated over 0.8 g of 10% strength palladium-on-charcoal under normal pressure in 200 ml of methanol, concentrated hydrochloric acid is added, the mixture is filtered, the filtrate is concentrated and the residue is stirred with diisopropyl ether. 8.5 g (97%) of 4-chlorodifluoromethoxy-1,2-phenylenediamine dihydrochloride are obtained.

d) 6.3 g (72%) of the title compound of m.p. 268-270°C (decomposition) are obtained from 8.5 g of the above compound analogously to Example 21e).

25. 5-Difluoromethoxy-2-mercapto-1H-benzimidazole

a) 11.8 g of N-(4-difluoromethoxyphenyl)-acetamide [L.M. Jagupol'skii et al., J.General Chemistry (USSR) 39, 190 (1969)] are stirred in 200 ml of dichloromethane with 12.1 ml of 100% strength nitric acid at room temperature for 1.5 hours. 13.3 g (92%) of N-[(4-difluoromethoxy-2-nitro)phenyl]-acetamide (m.p. 71-73°C) are obtained analogously to Example 21b).

b) 4-Difluoromethoxy-2-nitroaniline (m.p. 68-70°C) is obtained therefrom in 96% yield analogously to

Example 24b.

c) 4-Difluoromethoxy-1,2-phenylenediamine dihydrochloride is obtained therefrom in 94% yield analogously to Example 24c.

d) The title compound of m.p. 250-252°C (from isopropanol) is obtained in 78% yield analogously to Example 21e:

26. 5,6-Bis(difluoromethoxy)-2-mercapto-1H-benzimidazole

a) 275 g of chlorodifluoromethane are passed into a solution of 100 g of pyrocatechol, 220 g of sodium hydroxide and 60 g of sodium dithionite in 500 ml of water and 400 ml of dioxane at 50-55°C analogously to L.N. Sedova et al., Zh. Org. Khim. 6, 568 (1970). After distillation at 61-62°C/1.0-1.1 kPa, a mixture of 1,2-bis(difluoromethoxy)benzene and 2-difluoromethoxyphenol is obtained, the products being separated by chromatography on silica gel by means of cyclohexane/ethyl acetate (4:1).

b) A solution of 15 g of 1,2-bis(difluoromethoxy)-benzene and 15 ml of 100% pure nitric acid in 150 ml of dichloromethane is stirred at room temperature for 7 hours. The mixture is neutralized with potassium bicarbonate solution and the organic layer is separated off and chromatographed on silica gel by means of cyclohexane/ethyl acetate (4:1). 1,2-Bis(difluoromethoxy)-4-nitrobenzene is obtained. This is hydrogenated and acetylated analogously to Example 21a to give N-[3,4-bis(difluoromethoxy)phenyl]acetamide (m.p. 81-83°C). Analogously to Example 21, furthermore, N-[4,5-bis(difluoromethoxy)-2-nitrophenyl]acetamide (m.p. 65-67°C), N-[4,5-bis(difluoromethoxy)-2-nitro]aniline (m.p. 107-109°C), 4,5-bis-(difluoromethoxy)-1,2-phenylenediamine dihydrochloride and the title compound of m.p. 285-287°C (decomposition; from isopropanol) are obtained.

27. 5-Difluoromethoxy-2-mercapto-6-methoxy-1H-benzimidazole

a). About 58 g of chlorodifluoromethane are passed into a solution of 55.5 g of guaiacol and 130 g of sodium

hydroxide in 300 ml of water and 300 ml of dioxane at 60°C. The mixture is filtered at 10°C and the organic layer is separated off, dried with anhydrous potassium carbonate and distilled. 56 g (73%) of 1-difluoromethoxy-2-methoxybenzene of boiling point 75-76°C/0.9 kPa are obtained.

b) A solution of 33.8 ml of 100% strength nitric acid in 90 ml of dichloromethane is added dropwise to a solution of 47 g of the above compound in 230 ml of dichloromethane at 0-5°C, 250 ml of ice-water are added after 30 minutes and the mixture is neutralized with potassium bicarbonate. The dried organic phase is concentrated in vacuo and the residue is recrystallized from cyclohexane. 53 g (90%) of 1-difluoromethoxy-2-methoxy-5-nitrobenzene (m.p. 48-49°C) are obtained. This is hydrogenated and acetylated analogously to Example 21a. N-(3-Difluoromethoxy-4-methoxyphenyl)acetamide (m.p. 129-130°C) is obtained in 90% yield.

c) 46 g of the above compound are nitrated with 33 ml of 100% strength nitric acid in dichloromethane analogously to the above instructions. N-(5-Difluoromethoxy-4-methoxy-2-nitrophenyl)acetamide (m.p. 116-117°C) is obtained in 99% yield.

d) 54 g of the above compound are stirred in 810 ml of methanol with 44.8 ml of 30% strength methanolic sodium methylate solution at room temperature for 1 hour. The mixture is concentrated in vacuo and ice-water and glacial acetic acid are added to pH 8 to give 5-difluoromethoxy-4-methoxy-2-nitroaniline (m.p. 144-145°C) in 99% yield.

e) 25 g of the above compound are hydrogenated in 300 ml of methanol over 1.25 g of 10% strength palladium-on-charcoal in accordance with Example 21d. 26 g (88%) of 3-difluoromethoxy-4-methoxy-1,2-phenylenediamine dihydrochloride of m.p. 218-220°C (decomposition) are obtained.

f) 25 g of the above compound are reacted with 19 g of potassium O-ethyldithiocarbonate in accordance with

Example 21e. 20 g (89%) of the title compound of m.p. 280-282°C (decomposition; from isopropanol) are obtained.

28. 5-Difluoromethoxy-6-fluoro-2-mercapto-1H-benzimidazole

a) 1-Difluoromethoxy-2-fluorobenzene (b.p. 76°C/10 kPa; n_D^{20} = 1.4340) is obtained analogously to Example 27a from 2-fluorophenol and chlorodifluoromethane.

b) 38.4 ml of 100% strength nitric acid are added dropwise to 30 g of the above compound in 300 ml of dichloromethane at -10°C and the mixture is stirred at -10°C for 1 hour and at 0°C for 2.5 hours. Ice-water is added and the mixture is rendered neutral and chromatographed over silica gel with ethyl acetate/cyclohexane (4:1). 34 g of an oil are obtained, which contains about 90% of 1-difluoromethoxy-2-fluoro-4-nitrobenzene and 10% of 1-difluoromethoxy-2-fluoro-5-nitrobenzene (NMR spectrum).

c) 30 g of the above mixture are hydrogenated and acetylated analogously to Example 21a. Recrystallization from toluene gives 21 g (65%) of N-(4-difluoromethoxy-3-fluorophenyl)acetamide of m.p. 112-113°C.

d) 22.5 ml of 100% strength nitric acid are added dropwise to 20 g of the above compound in 200 ml of dichloromethane at 20°C in the course of 30 minutes and the mixture is subsequently stirred at room temperature for 15 hours. N-(4-difluoromethoxy-5-fluoro-2-nitrophenyl)acetamide of m.p. 72-74°C (from cyclohexane) is obtained in 89% yield analogously to Example 27c. Stirring with 1 M hydrochloric acid in methanol at 60°C for several hours gives 4-difluoromethoxy-5-fluoro-2-nitroaniline of m.p. 95-97.5°C in 95% yield and, analogously to Example 27e), 4-difluoromethoxy-5-fluoro-1,2-phenylenediamine dihydrochloride in 85% yield. Decomposition from 210°C.

e) 15 g of the above compound are reacted with 11.8 g of potassium O-ethyldithiocarbonate in accordance with Example 21e. 11.1 g (84%) of the title compound of m.p. 275-276°C (decomposition, from isopropanol) are obtained.

29. 2,2-Difluoro-5H-[1,3]-dioxolo[4,5-f]benzimidazole-6-thiol

a) 30 g of 4-amino-2,2-difluoro-5-nitro-1,3-benzodioxole in 300 ml of methanol are hydrogenated over 0.5 g of 10% strength palladium-on-charcoal in a circulatory hydrogenation apparatus under atmospheric pressure at room temperature, 2.5 equivalents of methanolic hydrogen chloride solution are added, the mixture is filtered, the solution is concentrated in vacuo and isopropanol and ether are added to the residue to give 35 g (97%) of 2,2-difluoro-1,3-benzodioxole-4,5-diamine dihydrochloride of m.p. 232-233°C (decomposition).

b) 24 g of potassium O-ethyldithiocarbonate (recrystallized from isopropanol) and 9.2 g of sodium hydroxide in 55 ml of water are added to 30 g of the above compound in 300 ml of ethanol and the mixture is heated to the boiling point under reflux for 15 hours. The mixture is poured onto 1.5 l of water, brought to pH 14 with sodium hydroxide solution, clarified with active charcoal and precipitated with concentrated hydrochloric acid under the influence of heat and the precipitate is filtered off with suction in the cold. 24 g (91%) of the title compound of m.p. 365-370°C (decomposition) are obtained.

30. 6,6,7-Trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]-benzimidazole-2-thiol

a) A mixture of 39.5 ml of 69% strength nitric acid and 46 ml of 97% strength sulfuric acid is added dropwise to 50 g of 2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine at 5°C in the course of 1 hour. The mixture is stirred at 10°C for 1 hour, at 20°C for 1 hour and at 40°C for 5 minutes, poured onto 200 g of ice and extracted with dichloromethane and the extract is washed with water, dried with magnesium sulfate and distilled in vacuo. 58 g (94%) of a mixture of 2,2,3-trifluoro-2,3-dihydro-6-nitro-(and 7-nitro)-1,4-benzodioxine of b.p. 68.5°C (0.15 mbar) and n_D^{20} 1.5080 are obtained. A gas chromatogram with a 10 m fused silica column (Chrompack) shows

two peaks in the ratio 2:3.

b) 35 g of the isomer mixture are hydrogenated in 400 ml of ethanol over 3 g of 10% strength palladium-on-charcoal under atmospheric pressure at 20-30°C in a circulatory hydrogenation apparatus, the mixture is filtered and the filtrate is concentrated in vacuo. 30.5 g (100%) of a liquid mixture of 6-amino-(and 7-amino)-2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine are obtained.

c) A mixture of 15.3 g of acetic anhydride and 15 ml of glacial acetic acid is added dropwise to 28 g of the above isomer mixture at 20-30°C, the mixture is stirred at 30°C for 30 minutes, 1 ml of water is added, the mixture is stirred at 30°C for 30 minutes and the solvent is distilled off in vacuo. Recrystallization from toluene gives 19 g of a fraction of a mixture of the isomeric acetamino derivatives of m.p. 128-133°C.

d) 14 ml of 100% strength nitric acid, dissolved in 60 ml of dichloromethane, are added dropwise to 17 g of the isomer mixture of the acetamino derivatives, suspended in 200 ml of dichloromethane, at -6° to -8°C and the mixture is stirred at 0°C for 2 hours and then at room temperature overnight. The mixture is poured onto 110 g of ice and the organic phase is separated off, washed with water and concentrated in vacuo. The residue (19.8 g) is recrystallized from 20 ml of ethanol. 15.5 g of a mixture of 6-acetamino-2,2,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-acetamino-2,2,3-trifluoro-2,3-dihydro-6-nitro-1,4-benzodioxine are obtained.

e) 14.5 g of the above product mixture are suspended in 80 ml of methanol, and 30 ml of 5M sodium hydroxide solution are added dropwise, while warming to 30°C. The mixture is stirred at room temperature for a further 0.5 hour and poured onto 200 g of ice to give 11.7 g of a mixture of 6-amino-2,2,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-amino-2,2,3-trifluoro-2,3-dihydro-6-nitro-1,4-benzodioxine. A sample is separated on a silica gel column with cyclohexane/ethyl acetate (4:1) into two pure isomers of melting points 110.5-111.5°C and

120-121°C, the NMR spectra of which on a 60 MHz instrument in deuterochloroform are virtually identical.

f) 10.9 g of the above isomer mixture are hydrogenated in 300 ml of methanol at room temperature under atmospheric pressure over 1 g of 10% strength palladium-on-charcoal in the course of 2.5 hours. 30 ml of 4 M hydrogen chloride in methanol are added, the mixture is filtered, the filtrate is concentrated in vacuo and the residue is stirred with 100 ml of ether. 12.6 g (98%) of 2,2,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6,7-diamine dihydrochloride (m.p. >250°C) are obtained.

g) 20.5 ml of 4 M aqueous potassium hydroxide solution are added to 12 g of the above compound and 8.5 g of potassium O-ethyldithiocarbonate (recrystallized from isopropanol) in 120 ml of ethanol and the mixture is heated to the boiling point under reflux for 17 hours. The mixture is poured onto 300 g of ice, brought to pH 12-13 with potassium hydroxide solution, clarified with active charcoal and precipitated with concentrated hydrochloric acid. Renewed precipitation with acid from alkaline aqueous-alcoholic solution gives 10 g (93%) of the title compound of m.p. 309-310°C (decomposition).

31. <u>6-Chloro-6,7,7-trifluoro-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazole-2-thiol</u>

a) A mixture of 18.3 ml of 65% strength nitric acid and 15.4 ml of 97% strength sulfuric acid is added dropwise to 18 g of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine at 5°C and the mixture is stirred at 5-10°C for 2 hours and poured onto ice. It is extracted with methylene chloride to give 21.3 g of a mixture of 2-chloro-2,3,3-trifluoro-2,3-dihydro-6-nitro-(and 7-nitro)-1,4-benzodioxine as an oil.

b) An oily mixture of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6-(and 7-)amine is obtained therefrom in 95% yield analogously to Example 30b), which is reacted quantitatively to give a mixture of the corresponding acetamino derivatives in accordance with Example 30c).

c) 19 g of the above mixture are stirred in 190 ml of dichloromethane with 16 ml of 100% strength nitric acid and the reaction product is purified by chromatography on silica gel by means of cyclohexane/ethyl acetate (4:1). 15 g of a mixture of 6-acetamino-2-chloro-2,3,3-trifluoro-6,7-dihydro-7-nitro-1,4-benzodioxine and 7-acetamino-2-chloro-2,3,3-trifluoro-6,7-dihydro-6-nitro-1,4-benzodioxine are obtained as a pale yellow oil.

d) 10.2 ml of a 30% strength solution of sodium methylate in methanol are added dropwise to 14.5 g of the above mixture in 100 ml of methanol at 5°C, the mixture is stirred for 1.5 hours, without cooling, poured onto ice, neutralized with dilute hydrochloric acid and extracted with dichloromethane and the extract is concentrated in vacuo. 12.7 g of a mixture of 6-amino-2-chloro-2,3,3-trifluoro-2,3-dihydro-7-nitro-1,4-benzodioxine and 7-amino-2-chloro-2,3,3-trifluoro-2,3-dihydro-6-nitro-1,4-benzodioxine are obtained as an orange-colored oil.

e) 12.4 g of the above mixture are hydrogenated analogously to Example 30f). 12.6 g (99%) of 2-chloro-2,3,3-trifluoro-2,3-dihydro-1,4-benzodioxine-6,7-diamine dihydrochloride are obtained.

f) 12.4 g of the above compound are reacted with 9.1 g of potasium O-ethyldithiocarbonate and potassium hydroxide solution in ethanol analogously to Example 30g). 9.6 g (74%) of the title compound of m.p. 288-290°C (decomposition) are obtained.

32. <u>2-Chloromethyl-4,5-dimethoxy-pyridinium chloride</u>

a) 2-Chloromethyl-4,5-dimethoxy-pyridinium chloride

3 ml of thionyl chloride, dissolved in 10 ml of methylene chloride, are added dropwise to a solution, cooled to 0°C, of 5 g of 2-hydroxymethyl-4,5-dimethoxy-pyridine in 40 ml of methylene chloride in the course of one hour, the reaction mixture is then stirred at 20°C for 4 hours, during which it becomes red-colored, 5 ml of toluene are added and the mixture is concentrated completely on a rotary evaporator (30°C/5 mbar). The oily

residue is dissolved in 50 ml of warm isopropanol and the solution is clarified with a little Tonsil®, filtered and concentrated again. The residue is taken up in 10 ml of toluene and the solution is made to crystallize with petroleum ether. After cooling in an ice-bath, the precipitate is filtered off with suction, washed with petroleum ether and dried. 4.6 g (70% of theory) of the title compound 2-chloromethyl-4,5-dimethoxy-pyridinium chloride are obtained as a colorless solid; decomp. at 160-61°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-pyridine

19 g of 4,5-dimethoxy-2-methylpyridine 1-oxide are metered into 60 ml of acetic anhydride, warmed to 80°C, in the course of 30 minutes in a manner such that the temperature does not rise above 100°C. After a further 45 minutes at 85°C, excess acetic anhydride is distilled off in vacuo and the oily dark residue, which essentially consists of the intermediate 2-acetoxymethyl-4,5-dimethoxypyridine is stirred with 80 ml of 2N sodium hydroxide solution at 80°C for 1 hour. After dilution with 80 ml of water and cooling, the mixture is extracted eight times with 100 ml of methylene chloride each time, the combined organic phases are washed twice with 1N sodium hydroxide solution, dried and concentrated and the crystalline, brownish residue is recrystallized from toluene. 14 g (74% of theory) of 2-hydroxymethyl-4,5-dimethoxy-pyridine of m.p. 122-24°C are obtained.

c) 4,5-Dimethoxy-2-methylpyridine 1-oxide

20 ml of a 30% strength sodium methylate solution are added dropwise to a suspension of 16.9 g of 5-methoxy-2-methyl-4-nitropyridine 1-oxide in 170 ml of dry methanol and the mixture is stirred at 20°C for 15 hours and then at 50°C for 4 hours. The pH is brought to 7 by careful addition of concentrated sulfuric acid, while cooling with ice, the mixture is concentrated, the residue is extracted by stirring with 200 ml of methylene chloride, the insoluble constituents are filtered off, 10 ml of toluene are added and the mixture is concentrated to

dryness again. 15.2 g (98% of theory) of 4,5-dimethoxy-2-methylpyridine 1-oxide are obtained as colorless crystals of m.p. 118-121°C.

d) 5-Methoxy-2-methyl-4-nitropyridine 1-oxide

21.2 g of 5-methoxy-2-methylpyridine 1-oxide are metered into 35 ml of 65% strength nitric acid, warmed to 60°C, in a manner such that the temperature of the reaction mixture does not rise above 80°C. The mixture is stirred at 80°C for 1 hour, a further 13 ml of 100% strength nitric acid are added to bring the reaction to completion and the mixture is stirred at 60-70°C for a further 2 hours. For working up, the mixture is poured onto 300 g of ice. The yellow precipitate which has separated out is filtered off over a suction filter, washed with water and dried. The dry solid is boiled up with 200 ml of methylene chloride, filtered off and dried. Further TLC-pure product is isolated by concentration of the filtrate. 22.3 g (87% of theory) of 5-methoxy-2-methyl-4-nitropyridine 1-oxide of m.p. 201-202°C are obtained; yellow crystals.

e) 5-Methoxy-2-methylpyridine 1-oxide

120 g of 30% strength hydrogen peroxide solution are added dropwise to a solution of 60.9 g of 5-methoxy-2-methylpyridine in 300 ml of glacial acetic acid at 60°C in the course of 1 hour and the mixture is subsequently stirred for 3 hours. After destruction of excess per-compounds by addition of active manganese dioxide, the mixture is filtered, the filtrate is concentrated, the residue is clarified hot in 500 ml of ethyl acetate, the mixture is concentrated again and the residue is distilled under 0.3 mbar. 54 g (77% of theory) of 5-methoxy-2-methylpyridine 1-oxide are obtained as a rapidly solidifying oil (b.p. 130°C); m.p. 80-84°C.

f) 5-Methoxy-2-methylpyridine

150 ml of 3-hydroxy-6-methylpyridine are metered into a solution of 84 g of potassium hydroxide in 400 ml of methanol and 500 ml of dimethyl sulfoxide in the course of one hour. After removal of the methanol on a rotary

evaporator, 213 g of methyl iodide, dissolved in 100 ml of dimethyl sulfoxide, are added dropwise, while cooling with ice, and the reaction mixture is stirred at 20°C for 15 hours and subjected to steam distillation. The distillate is extracted continuously in the extractor with methylene chloride and the extract is concentrated. 85 g (56% of theory) of 5-methoxy-2-methylpyridine are obtained as a colorless oil.

33. 2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride

a) 2-Chloromethyl-4,5-dimethoxy-3-methylpyridinium chloride

3.45 g (99% of theory) of the title compound are obtained as colorless crystals by the procedure described in Example 32a) by reaction of 2.7 g of 2-hydroxymethyl-4,5-dimethoxy-3-methylpyridine with 4 g of thionyl chloride in 25 ml of methylene chloride, after a reaction time of 1 hour and after a simplified method of working up, in particular by addition of 10 ml of toluene, removal of the methylene chloride and excess thionyl chloride by distillation, removal of the crystals precipitated by filtration with suction and drying; decomp. at 125-26°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridine

4.5 g of 4,5-dimethoxy-2,3-dimethylpyridine 1-oxide are warmed to 110°C in 20 ml of acetic anhydride in the course of 30 minutes and the mixture is then concentrated on a rotary evaporator. The oily residue, which consists of the intermediate 2-acetoxymethyl-4,5-dimethoxy-3-methylpyridine, is stirred in 30 ml of 3N sodium hydroxide solution at 80°C for 2 hours, the mixture is extracted, after cooling, five times with 30 ml of methylene chloride each time, the combined organic phases are washed twice with 2N sodium hydroxide solution, dried and concentrated and the residue is stirred with petroleum ether, filtered off with suction and dried. 4.0 g (89% of theory) of 2-hydroxymethyl-4,5-dimethoxy-3-methylpyridine of m.p. 91-92°C are obtained.

c) 4,5-Dimethoxy-2,3-dimethylpyridine 1-oxide

6.3 g of 4,5-dimethoxy-2,3-dimethylpyridine are dissolved in 120 ml of methylene chloride, 20 g of m-chloroperoxybenzoic acid are added successively and the mixture is stirred first at 20°C for 2 hours and then at 40°C for 4 hours. After addition of 20 ml of 5N sodium hydroxide solution, the mixture is washed three times with a mixture of 5% strength sodium thiosulfate solution and 5% strength sodium carbonate solution, the aqueous phase is back-extracted twice with methylene chloride and the combined organic phases are dried over magnesium sulfate and concentrated. 4.6 g (66% of theory) of 4,5-dimethoxy-2,3-dimethylpyridine 1-oxide are obtained. The Rf value in methylene chloride/methanol 19:1 is 0.25.

d) 4,5-Dimethoxy-2,3-dimethylpyridine

7.4 g (74% of theory) of 4,5-dimethoxy-2,3-dimethylpyridine are obtained as a colorless, gradually crystallizing oil of m.p. 36-38°C by the procedure described in Example 32f) by reaction of 9.18 g of 5-hydroxy-4-methoxy-2,3-dimethylpyridine in 50 ml of dimethyl sulfoxide first with 3.6 g of sodium hydroxide and then with 8.95 g of methyl iodide.

e) 5-Hydroxy-4-methoxy-2,3-dimethylpyridine

1,000 g of 4-methoxy-2,3-dimethylpyridine 1-oxide are metered into 3 l of acetic anhydride at 100°C in the course of 7 hours while stirring, and the mixture is subsequently stirred at 100°C for a further 3 hours. The mixture is allowed to cool and is concentrated completely at 70°C/10 mbar and the residue is then distilled under 10^{-2} mbar. The fraction with a boiling range from 95 to 145°C (mixture of the intermediate 5-acetoxy-4-methoxy-2,3-dimethylpyridine and 2-acetoxymethyl-4-methoxy-3-methylpyridine) is removed (952 g) and added to 3.5 l of 2N sodium hydroxide solution, warmed to 50°C, in the course of 30 minutes.

The mixture is stirred at 50°C until a clear solution is formed (about 3 hours) and is allowed to cool and is extracted three times with 1 l of methylene

chloride each time. The combined organic phases are back-extracted twice with 0.5 l of 1N sodium hydroxide solution each time and the combined aqueous phases are then brought to pH 7.5 with half-concentrated hydrochloric acid, with stirring. The solid which has precipitated out is filtered off, rinsed and dried to constant weight. 5-Hydroxy-4-methoxy-2,3-dimethylpyridine of m.p. 274-76°C is obtained.

34. 2-Chloromethyl-3,4-dimethoxy-pyridinium chloride

a) 2-Chloromethyl-3,4-dimethoxy-pyridinium chloride

4.2 g (93% of theory) of the title compound are obtained as a colorless solid of m.p. 151-152°C (decomp.) by the procedure described in Example 32a by reaction of 3.38 g of 2-hydroxymethyl-3,4-dimethoxypyridine with 2 ml of thionyl chloride in 30 ml of methylene chloride, after a reaction time of 2.5 hours and after the type of working up described in Example 33a.

b) 2-Hydroxymethyl-3,4-dimethoxypyridine

After adding 15 ml of 2N sodium hydroxide solution, 4.8 g of 2-acetoxymethyl-3,4-dimethoxypyridine are stirred vigorously at 80°C, whereupon a homogeneous solution forms from the initial two-phase mixture. After 2 hours, the solution is allowed to cool and is extracted five times with 30 ml of methylene chloride each time, the combined organic phases are washed twice with 5 ml of 0.3 N sodium hydroxide solution each time, dried over potassium carbonate, filtered and concentrated and the distillation residue is stirred with petroleum ether. 3.6 g (96% of theory) of 2-hydroxymethyl-3,4-dimethoxypyridine are obtained as a colorless solid of m.p. 87-89°C.

c) 2-Acetoxymethyl-3,4-dimethoxypyridine

4.8 g (28 mmol) of 3,4-dimethoxy-2-methylpyridine 1-oxide are metered into 25 ml of acetic anhydride at 85°C in the course of one hour, the mixture is stirred at the same temperature for one hour and concentrated completely in vacuo and the brown oily residue is distilled in a bulb tube distil under 1 Pa. 5.3 g (90% of

theory) of 2-acetoxymethyl-3,4-dimethoxypyridine are obtained; b.p. 125-130°C.

d) 3,4-Dimethoxy-2-methylpyridine 1-oxide

4.5 g (25 mmol) of 3-methoxy-2-methyl-4-nitropyridine 1-oxide are stirred at 40°C in 75 ml of dry methanol, after addition of 4.7 ml of 30% strength sodium methylate solution, for 16 hours. The mixture is then cooled, brought to pH 7 with concentrated sulfuric acid, filtered and concentrated completely in vacuo, the oily, reddish residue is taken up in 50 ml of toluene, the mixture is filtered again to remove insoluble constituents and the filtrate is concentrated to dryness. The yellow oily residue crystallizes on an ice-bath and is finally extracted by stirring with 30 ml of petroleum ether (50/70) at 40°C. Filtration and drying in a desiccator gives 5.2 g (88% of theory) of 3,4-dimethoxy-2-methylpyridine 1-oxide in the form of pale yellow crystals of m.p. 111-113°C.

e) 3-Methoxy-2-methyl-4-nitropyridine 1-oxide

8 ml of concentrated nitric acid are added in four portions of 2 ml each to 5.4 g of 3-methoxy-2-methylpyridine 1-oxide in 12 ml of glacial acetic acid at 80°C in the course of 6 hours, the mixture is stirred at the same temperature overnight, a further 8 ml of nitric acid are added in three portions in the course of 6 hours and the mixture is stirred for a further 15 hours. After cooling, the mixture is poured onto ice (40 g) and brought to pH 6 with 10N sodium hydroxide solution, the by-product (3-methoxy-2-methyl-4-nitropyridine) which has precipitated out is filtered off and the filtrate is extracted four times with 50 ml of methylene chloride. After drying, the combined organic phases are concentrated completely and the residue is recrystallized from a little methylene chloride/petroleum ether. 4.2 g (57% of theory) of the title compound are obtained in the form of yellow crystals of m.p. 103-104°C.

f) 3-Methoxy-2-methylpyridine 1-oxide

15.3 g (0.124 mole) of 3-methoxy-2-methylpyridine

are dissolved in 100 ml of glacial acetic acid, and 40 ml of 30% strength hydrogen peroxide are added in 4 portions at 80°C in the course of 6 hours. The mixture is stirred for a further three hours and then concentrated in vacuo (1.5 kPa), and two 50 ml portions of acetic acid are added, the mixture being concentrated completely after each addition. Following negative detection of per-compounds, the mixture is distilled in a bulb tube oven. The fraction which distils at 120°C (1.5 Pa) is precipitated by stirring in a little diethyl ether and the solid is filtered off and dried. 12 g (60% of theory) of 3-methoxy-2-methylpyridine 1-oxide are obtained in the form of colorless crystals of m.p. 72-78°C.

g) 3-Methoxy-2-methylpyridine

15.5 g (90% of theory) of 3-methoxy-2-methylpyridine are obtained as a colorless oil by the procedure described in Example 32f by reaction of 13.7 g (125 mmol) of 3-hydroxy-2-methylpyridine with 9.2 ml of methyl iodide, with the addition of 46 ml of 3M methanolic potassium hydroxide solution and after a reaction time of 3 hours.

Commercial applicability

The dialkoxypyridines of the general formula I and their salts have valuable pharmacological properties which render them commercially useful. They clearly inhibit the secretion of gastric acid in warm-blooded animals, and moreover exhibit an excellent protective action on the stomach and intestine in warm-blooded animals. This protective action on the stomach and intestine is already observed when doses which are below the doses which inhibit acid secretion are administered. The compounds according to the invention are furthermore distinguished by the absence of substantial side effects and by a wide therapeutic range.

"protection of the stomach and intestine" in this connection is understood as the prevention and treatment of gastrointestinal diseases, in particular gastrointestinal

inflammatory diseases and lesions (such as, for example, gastric ulcer, duodenal ulcer, gastritis and stomach irritation caused by hyperacidity or medicaments), which can be caused, for example, by microorganisms, bacterial toxins, medicaments (for example certain anti phlogistics and antirheumatics), chemicals (for example ethanol), gastric acid or stress situations.

Another advantage of the compounds according to the invention is their comparatively high chemical stability.

Surprisingly, the compounds according to the invention prove to be clearly superior in their excellent properties to the compounds known from the prior art. On the basis of these properties, the dialkoxypyridines and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of diseases of the stomach and intestine and those diseases based on excessive secretion of gastric juice.

The invention thus also relates to the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

The invention furthermore relates to the use of the compounds according to the invention for the preparation of medicaments which are used for the treatment and/or prophylaxis of the abovementioned diseases.

The invention also relates to medicaments which contain one or more dialkoxypyridines of the general formula I and/or their pharmacologically acceptable salts.

The medicaments are prepared by processes which are known per se and with which the expert is familiar. As medicaments, the pharmacologically active compounds (= active compounds) according to the invention are used either as such or, preferably, in combination with suitable pharmaceutical auxiliaries or carriers, in the form of tablets, coated tablets, capsules, suppositories, plasters (for example as TTS), emulsions, suspensions or solutions, the

content of active compound advantageously being between 0.1 and 95%.

The auxiliaries or carriers which are suitable for the desired medicament formulations are familiar to the expert, on the basis of his expert knowledge. Besides solvents, gel formers, suppository bases, tablet excipients and other active compound vehicles, it is possible to use, for example, antioxidants, dispersing agents, emulsifiers, antifoaming agents, flavor correctants, preservatives, solubilizing agents, colorants or, in particular, permeation promoters and complexing agents (for example cyclodextrins).

The active compounds can be administered orally, parenterally or percutaneously.

In general, it has proved advantageous in human medicine to administer the active compound or compounds, in the case of oral administration, in a daily dose of about 0.01 to about 20, preferably 0.05 to 5 and in particular 0.1 to 1.5 mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses, to achieve the desired result. In the case of parenteral treatment, similar or (in particular in the case of intravenous administration of the active compound) as a rule lower dosages can be used. The particular optimum dosage and mode of administration of the active compounds required can easily be determined by any expert on the basis of his expert knowledge.

If the compounds and/or salts according to the invention are to be employed for the treatment of the abovementioned diseases, the pharmaceutical formulations can also contain one or more pharmacologically active constituents from other groups of medicaments, such as antacids, for example aluminum hydroxide and magnesium aluminate; tranquilizers, such as benzodiazepines, for example diazepam; spasmolytics, such as, for example, bietamiverine and camylofin; anticholinergics, such as, for example, oxyphencyclimine and phencarbamide; local anesthetics, such as, for example tetracaine and

procaine; and if appropriate also enzymes, vitamins or amino acids.

In this connection, combination of the compounds according to the invention with other drugs which inhibit acid secretion, such as, for example, H_2-blockers (for example cimetidine and ranitidine), and furthermore with so-called peripheral anticholinergics (for example pirenzepine, telenzepine and zolenzepine) and with gastrin antagonists with the aim of intensifying the main action in the additive or superadditive sense and/or eliminating or reducing side effects is to be particularly emphasized.

Pharmacology

The excellent protective action on the stomach and the inhibiting action on gastric secretion of the compounds according to the invention can be demonstrated in animal experiments using the model of Shay rats. The compounds according to the invention investigated have been given numbers as follows:

Serial No.	Name of the compound
1	2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole
2	2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole
3	2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
4	2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)-methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
5	2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)-methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]-benzimidazole

The influence of the compounds investigated on the formation of gastric lesions triggered off by pylorus ligature (4 hours; so-called Shay rats) and oral administration of 100 mg/kg of acetylsalicylic acid and on the

gastric secretion (HCl) in the rats over 4 hours is shown in the following table.

Protective action on the stomach and inhibition of gastric secretion

Serial No.	n [Number of animals]	Protective action on the stomach (rats) inhibition of the lesion index ED50+) [mg/kg, p.o.]	Inhibition of the HCl secretion in the stomach (rats; total of 4 hours) % inhibition of HCl secretion ++)	ED25+) [mg/kg, p.o.]	ED50+) [mg/kg, p.o.]
1	40	0.6	15	1.0	~ 3
2	48	0.8	25	0.7	1.7
3	56	0.6	18	~ 1	3.4
4	40	3.5	28	3.0	6.5
5	72	~ 1	25	1.0	3.0

+) ED25 and ED50 = dose which reduces the lesion index or the HCl secretion (4 hours) in the rat stomach by 25 and, respectively, 50% in the treated group in comparison with the control group.

++) after administration of the antiulcerous ED50

The antiulcerogenic action was tested by the so-called Shay rat method:

Ulcers are provoked in rats which have been kept in the fasting state for 24 hours (female, 180-200 g, 4 animals per cage on a high grid) by pylorus ligature (under diethyl ether anesthesia) and oral administration of 100 mg/10 ml/kg of acetylsalicylic acid. The substances to be tested are administered orally (10 ml/kg) one hour before the pylorus ligature. The wound is closed by means of Michel clamps. 4 hours thereafter, the animals are sacrificed under ether anesthesia by atlas dislocation and the stomach is resected. The stomach is opened longitudinally and fixed to a cork plate, after first the amount of secreted gastric juice (volume) and later its HCl content (titration with sodium

hydroxide solution) have been determined; the number and size (= diameter) of the ulcers present are determined with a stereomicroscope in 10-fold magnification. The product of the degree of severity (according to the following points scale) and number of ulcers serves as the individual lesion index.

Points scale:

no ulcers		0
ulcer diameter	0.1 - 1.4 mm	1
	1.5 - 2.4 mm	2
	2.5 - 3.4 mm	3
	3.5 - 4.4 mm	4
	4.5 - 5.4 mm	5
	> 5.5 mm	6

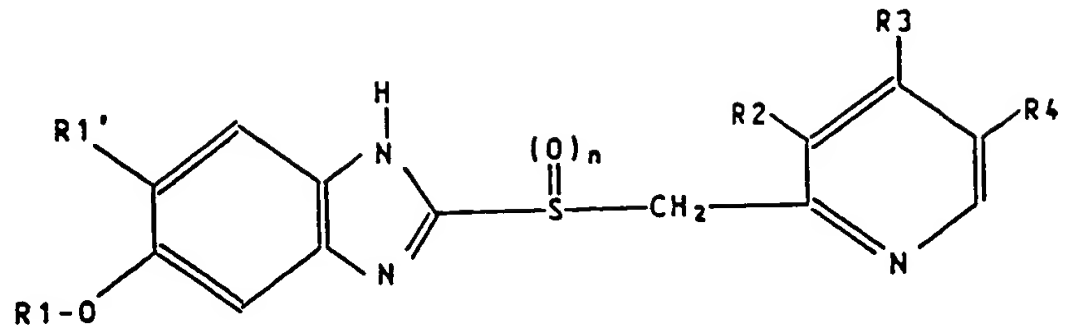
The reduction in the average lesion index of each treated group in comparison with that of the control group (= 100%) serves as a measure of the antiulcerogenic effect. The ED25 and ED50 designate those doses which reduce the average lesion index and the HCl secretion by 25% and, respectively, 50% in comparison with the control.

Toxicity

The LD50 of all the compounds tested is above 1,000 mg/kg [p.o.] in mice.

Patent Claims

1. Dialkoxypyridines of the general formula I



(I),

wherein

R1 represents a 1-3C-alkyl radical which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical and

R1' represents a hydrogen atom or a halogen atom, trifluoromethyl, a 1-3C-alkyl radical, or a 1-3C-alkoxy radical which is optionally completely or predominantly substituted by fluorine, or

R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is optionally completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,

R3 represents a 1-3C-alkoxy radical,

one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

n represents the numbers 0 or 1,

and the salts of these compounds.

2. Compounds of the general formula I according to claim 1, wherein

R1 represents a 1-3C-alkyl radical which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical,

R1' represents a hydrogen atom or a halogen atom, trifluoromethyl, a 1-3C-alkyl radical, or a 1-3C-alkoxy radical which is optionally completely or predominantly substituted by fluorine,

R3 represents a 1-3C-alkoxy radical,

one of the radical R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

n represents the numbers 0 or 1,

and the salts of these compounds.

3. Compounds of the general formula I according to claim 1, wherein

R1 and R1' together and with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is optionally completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,

R3 represents a 1-3C-alkoxy radical,

one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

n represents the numbers 0 or 1,

and the salts of these compounds.

4. Compounds of the general formula I according to claim 2, wherein

R1 represents 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl or difluoromethyl,

R1' represents a hydrogen atom,

R3 represents methoxy,

one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and

n represents the numbers 0 or 1,

and the salts of these compounds.

5. Compounds of the general formula I according to claim 3, wherein

R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a difluoromethylenedioxy radical or a metylenedioxy radical,

R3 represents methoxy,

one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and

n r presents the numbers 0 or 1,

and the salts of these compounds.

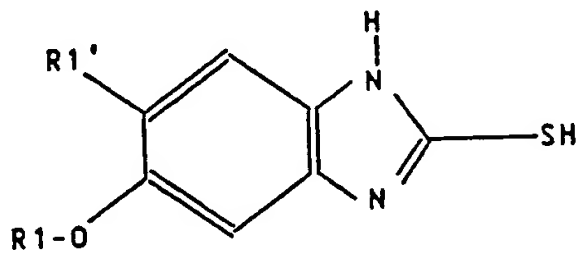
6. Compounds of the general formula I acc rding to one of claims 1 to 5, wherein n denotes the number 0, and th ir acid addition salts.

7. Compounds of the general formula I according to one of claims 1 to 5, wherein n denotes the number 1, and their salts with bases.

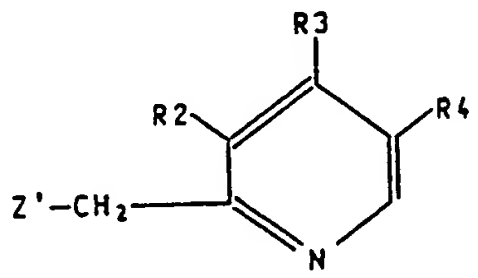
8. A compound chosen from the group consisting of 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole, 2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2,-tetrafluoroethoxy)-1H-benzimidazole, 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazole and 2,2-difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole and their salts.

9. Process for the preparation of dialkoxypyridines of the general formula I according to claim 1 and their salts, characterized in that

a) mercaptobenzimidazoles of the general formula II are reacted with picoline derivatives III,



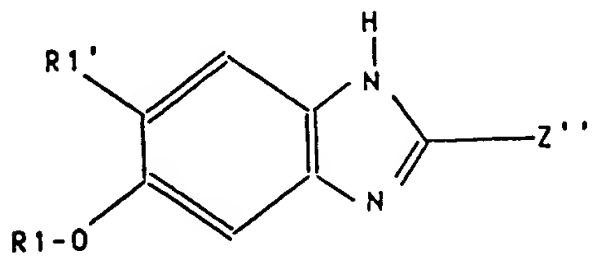
(II)



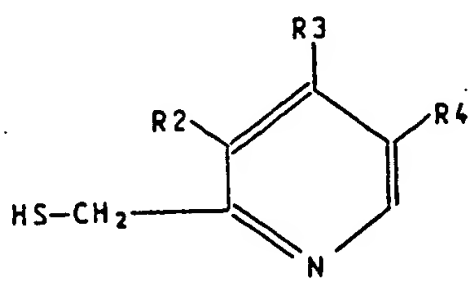
(III),

or

b) benzimidazoles of the general formula IV are reacted with mercaptopicolines V,



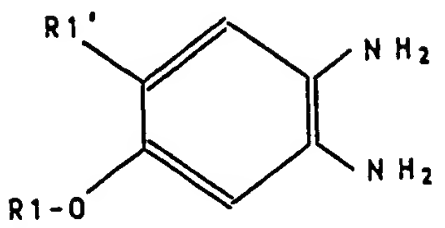
(IV)



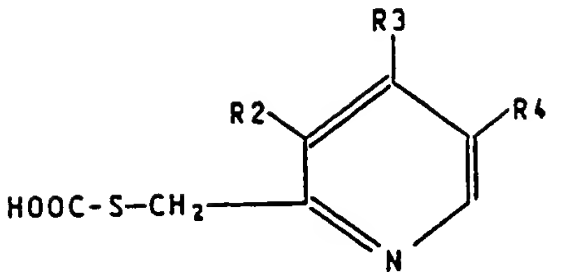
(V),

or

c) o-phenylenediamines of the general formula VI are reacted with formic acid derivatives VII

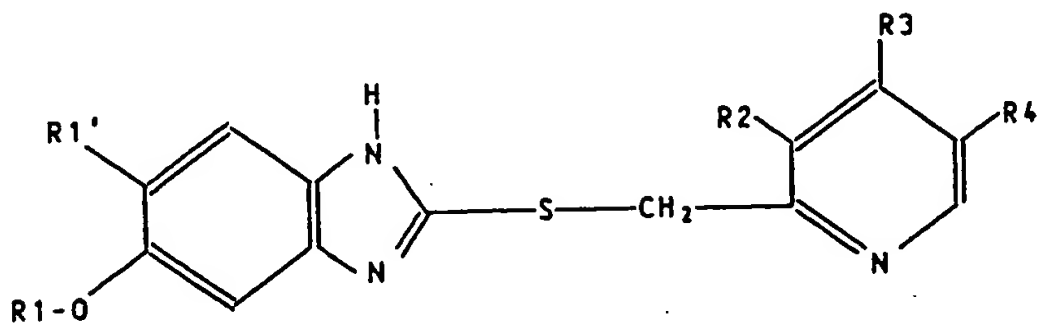


(VI)



(VII),

and the 2-benzimidazolyl 2-pyridylmethylsulfides of the general formula VIII obtained according to a), b) or c)

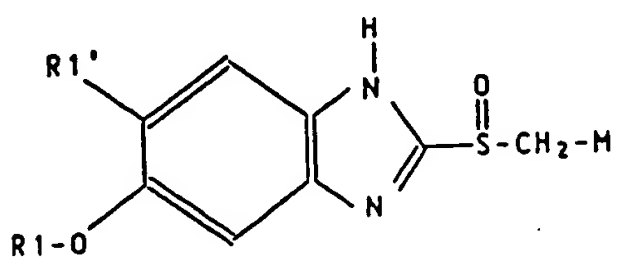


(VIII),

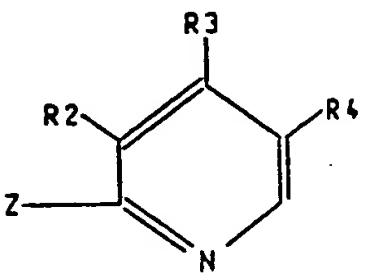
are then optionally oxidized and/or converted into the salts,

or

d) benzimidazoles of the general formula IX are reacted with pyridine derivatives X



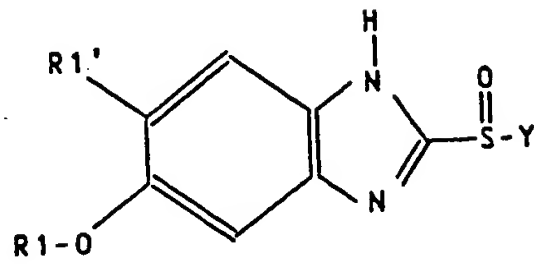
(IX)



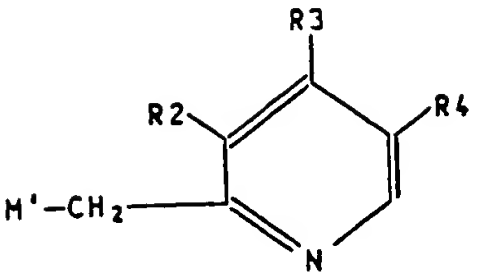
(X),

or

e) sulfinyl derivatives of the general formula XI are reacted with 2-picoline derivatives XII



(XI)



(XII),

and are then optionally subsequently converted into the salts, Y, Z, Z' and Z'' representing suitable leaving groups, M representing an alkali metal atom (Li, Na or K), M' representing the equivalent of a metal atom and R1, R1', R2, R3, R4 and n having the meanings given in claim 1.

10. Medicaments containing one or more dialkoxypyridines according to one or more of the claims 1 to 8 and/or their pharmacologically acceptable salts.

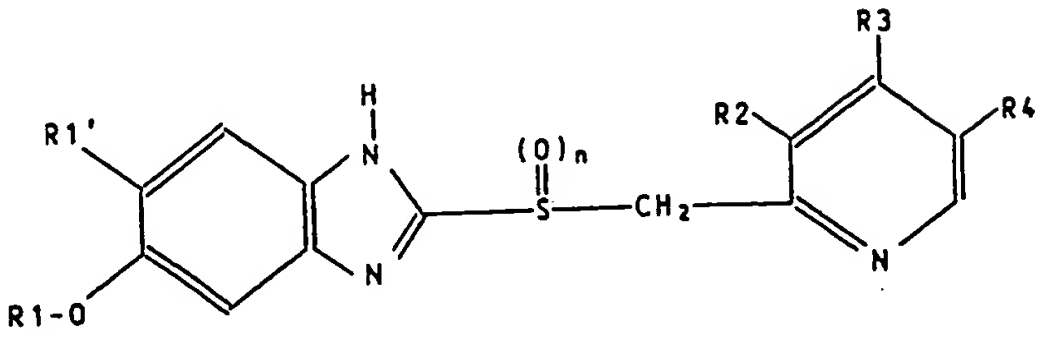
11. Dialkoxypyridines according to one of claims 1 to 8 and their pharmacologically acceptable salts for use in the treatment and/or prophylaxis of diseases of the stomach and/or intestine and diseases based on increased secretion of gastric acid.

12. Use of dialkoxypyridines according to one of claim 1 to 8 and their pharmacologically acceptable salts for the manufacture of medicaments for the treatment and/or prophylaxis of diseases of the stomach and/or intestine and diseases based on increased secretion of gastric acid.

13. 5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and its salts.

Patent Claims for the contracting state: AT

1. Process for the preparation of dialkoxypyridines of the general formula I



(I),

wherein

R1 represents a 1-3C-alkyl radical which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical and

R1' represents a hydrogen atom or a halogen atom, trifluoromethyl, a 1-3C-alkyl radical, or a 1-3C-alkoxy radical which is optionally completely or predominantly substituted by fluorine, or

R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is optionally completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,

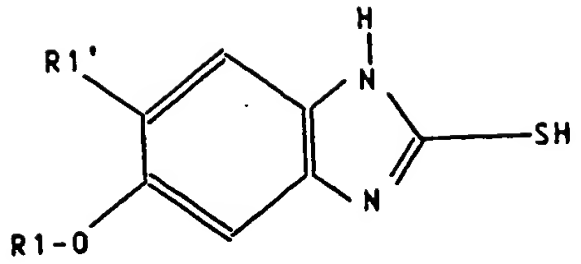
R3 represents a 1-3C-alkoxy radical,

one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

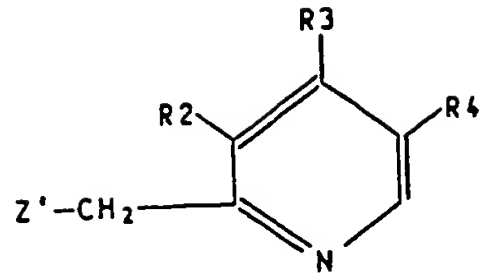
n represents the numbers 0 or 1,

and their salts, characterized in that

a) mercaptobenzimidazoles of the general formula II are reacted with picoline derivatives III,



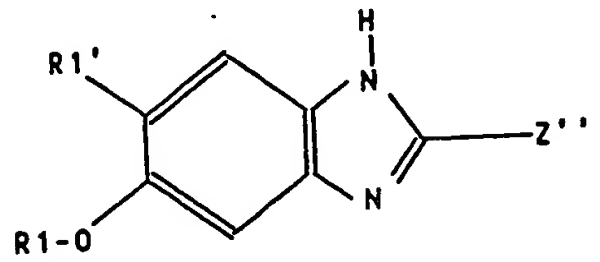
(II)



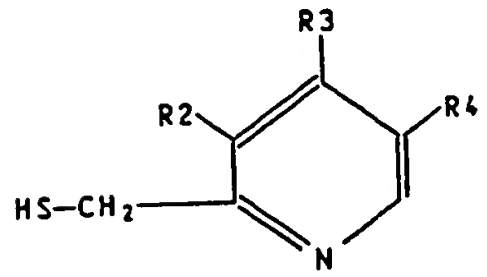
(III),

or

b) benzimidazoles of the general formula IV are reacted with mercapto-picolines V,



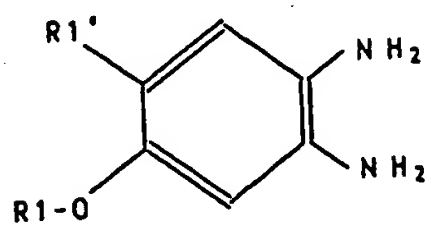
(IV)



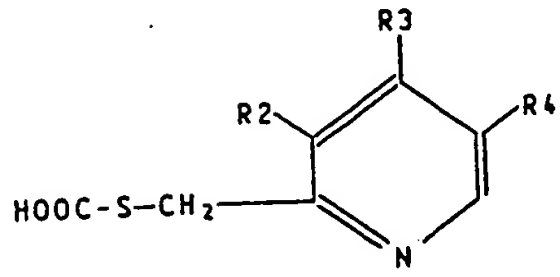
(V),

or

c) o-phenylenediamines of the general formula VI are reacted with f rmic acid derivatives VII

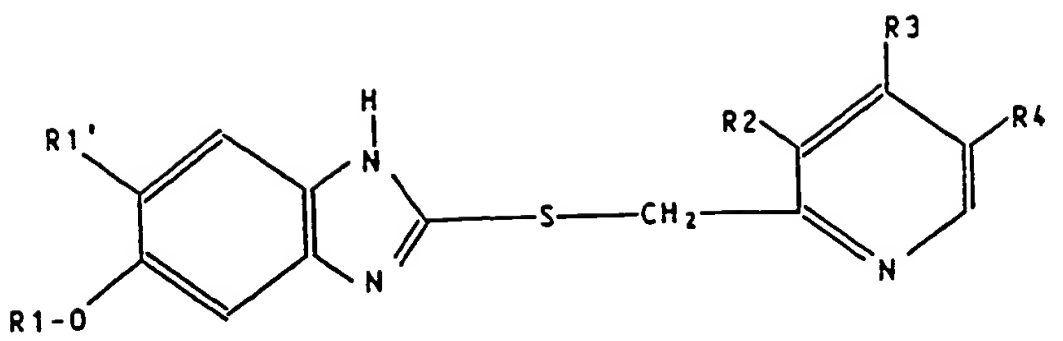


(VI)



(VII),

and the 2-benzimidazolyl 2-pyridylmethylsulfides of the general formula VIII obtained according to a), b) or c)

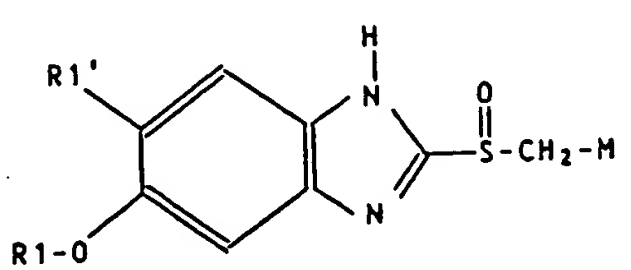


(VIII),

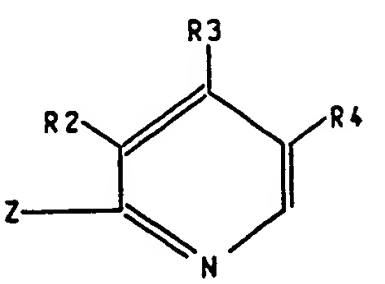
are then optionally oxidized and/or converted into the salts,

or

d) benzimidazoles of the general formula IX are reacted with pyridine derivatives X



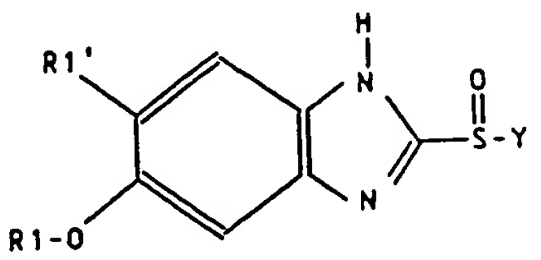
(IX)



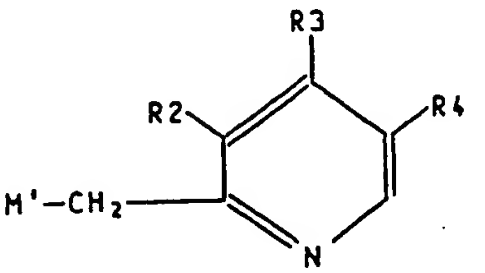
(X),

or

e) sulfinyl derivatives of the general formula XI are reacted with 2-picoline derivatives XII



(XI)



(XII),

and are then optionally subsequently converted into the salts, Y, Z, Z' and Z'' representing suitable leaving groups, M representing an alkali metal atom (Li, Na or K), M' representing the equivalent of a metal atom and R1, R1', R2, R3, R4 and n having the meanings given above.

2. Process according to claim 1, wherein

R1 represents a 1-3C-alkyl radical which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical,

R1' represents a hydrogen atom or a halogen atom, trifluoromethyl, a 1-3C-alkyl radical, or a 1-3C-alkoxy radical which is optionally completely or predominantly substituted by fluorine,

R3 represents a 1-3C-alkoxy radical,

one of the radical R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

n represents the numbers 0 or 1.

3. Process according to claim 1, wherein

R1 and R1' together and with inclusion of the oxygen atom to which R1 is bonded, represent a 1-2C-alkylenedioxy radical which is optionally completely or partly substituted by fluorine, or a chlorotrifluoroethylenedioxy radical,

R3 represents a 1-3C-alkoxy radical,

one of the radicals R2 and R4 represents a 1-3C-alkoxy radical and the other represents a hydrogen atom or a 1-3C-alkyl radical and

n represents the numbers 0 or 1.

4. Process according to claim 1, wherein

R1 represents 1,1,2,2-tetrafluoroethyl, trifluoromethyl, 2,2,2-trifluoroethyl or difluoromethyl,

R1' represents a hydrogen atom,

R3 represents methoxy,

one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom or methyl and

n represents the numbers 0 or 1.

5. Process according to claim 1, wherein

R1 and R1' together, with inclusion of the oxygen atom to which R1 is bonded, represent a difluoromethylenedioxy radical or a metylen dioxy radical,

R3 represents methoxy,

one of the radicals R2 and R4 represents methoxy and the other represents a hydrogen atom r methyl and

represents the numbers 0 or 1.

6. Process for the preparation of compounds of the general formula I according to claim 1, wherein R1, R1', R2, R3 and R4 have the meanings given in claim 1 and n represents the number 0, characterized in that mercaptobenzimidazoles of the gereral formula II are reacted with picoline derivatives III and are then optionally subsequently converted into the acid addition salts.

7. Process for the preparation of compounds of the general formula I according to claim 1, wherein R1, R1', R2, R3 and R4 have the meanings given in claim 1 and n represents the number 1, characterized in that the 2-benzimidazolyl 2-pyridylmethylsulfides of the general formula VIII are oxidized and are then optionally subsequently converted into the salts with bases.

8. Process for the preparation of medicaments, characterized in that a compound of the general formula I according to claim 1 or a pharmacologically acceptable salt thereof is mixed with a pharmaceutical auxiliary and/or carrier.

9. Process for the preparation of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and its salts, characterized in that 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole is oxidized and, if desired, the resulting 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole is subsequently converted into a salt.

10. Process for the preparation of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole and its salts, characterized in that 5-difluoromethoxy-2-mercapto-1H-benzimidazole is reacted with 2-chloromethyl-3,4-dimethoxypyridine or its salt, and, if desired, the resulting 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole is subsequently converted into a salt or a resulting salt of the 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazole is subsequently converted into the free compound.